JOC The Journal of Organic Chemistry

Article

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Diastereoselective Synthesis of C2′-Fluorinated Nucleoside Analogues Using an Acyclic Approach

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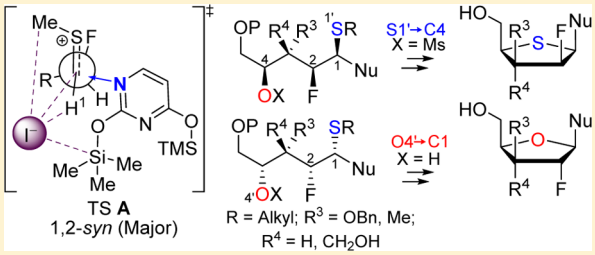
Supporting Information

ABSTRACT: Nucleoside analogues bearing a fluorine in the C2′-position have been synthesized by S_N2-like cyclizations of acyclic thioaminal precursors. This strategy provides access to two scaffolds, D-1′,2′-*cis*-thiofuranosides and D-1′,2′-*trans*-furanosides, which are difficult to generate using the standard approach for nucleoside synthesis. The addition of silylated nucleobases onto model C2-fluorinated dithioacetal substrates resulted in 1,2-*syn* diastereoselectivity, which is consistent with the C2−F and *S*-alkyl moiety being in close proximity. A new series of analogues bearing a C3′ all-carbon quaternary center along with a C2′−F atom have also been synthesized using this approach and are being investigated as potential antimetabolites.



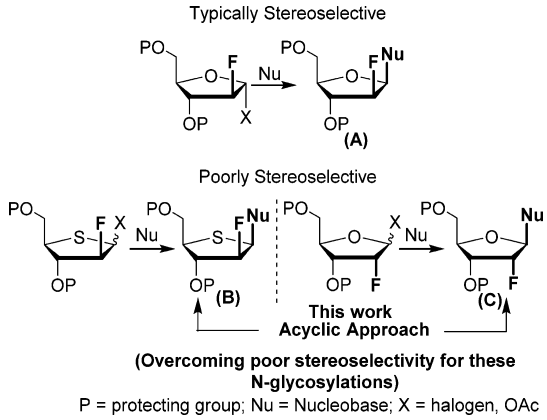
INTRODUCTION

Effective treatments against cancer and viral infections involve the administration of modified nucleosides (NAs: nucleoside analogues) that act as inhibitors of tumor growth and viral replication.[1] The synthesis of these molecules requires a stereocontrolled N-glycosylation reaction, which remains a challenge, especially when a fluorine atom is present at the C2′-position. This structural feature is found in several important FDA-approved anticancer (e.g., Clofarabine, Gemcitabine) and antiviral (e.g., Sofosbuvir) agents. Two main approaches exist to access these scaffolds involving either fluorination of natural nucleosides or nucleobase addition onto already fluorinated substrates.[2,3] The first approach allows for the original configuration of the glycosidic bond to be maintained and is limited to the natural pool of nucleosides. Alternatively, nucleobase addition onto substrates already possessing a C2−F group allows for increased substrate diversity, but the stereochemistry of the glycosidic bond needs to be controlled. Typically, a stereoselective 1′,2′-*cis* relationship between the nucleobase and the C2′−F group in the furanoside series (**A**) is obtained through displacement of anomeric halo sugars (Scheme 1).[2,4] However, to the best of our knowledge, no approach has been reported to provide high 1′,2′-*cis* selectivity in the corresponding thiofuranoside (**B**) series.[5−7] Thio scaffolds improve the pharmacokinetic profile of nucleoside analogues, as seen with T-AraC versus AraC, for solid tumors.[8,9]

Controlling the 1′,2′-*trans* stereochemistry (**C**) for C2′-monofluorinated NAs is also particularly challenging due to the lack of possible C2-neighboring group participation. Nucleobase addition results in variable 1′,2′-*trans* selectivity,[10−12] and their synthesis often relies on fluorination of preformed nucleoside analogues.[13−15]

These synthetic challenges highlight the need for a novel approach to access such scaffolds (Scheme 1). The acyclic methodology presented herein provides an efficient route for the formation of 1′,2′-*trans*-furanosides and 1′,2′-*cis*-thiofurano-

Scheme 1. Standard Approaches To Synthesize NAs bearing a C2′−F



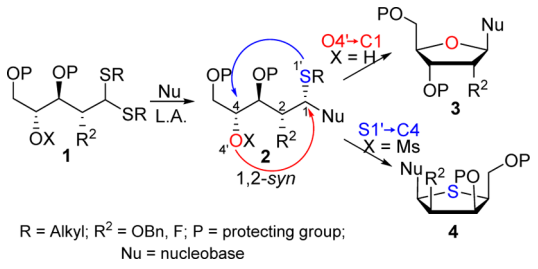
This work addresses the synthesis of two challenging scaffolds using the acyclic approach.

Received: July 29, 2016
Published: October 13, 2016

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

sides (Scheme 2). In the development of this approach, it was determined that silylated nucleobases add to C2-alkoxy

Scheme 2. Acyclic Strategy for the Synthesis of NAs



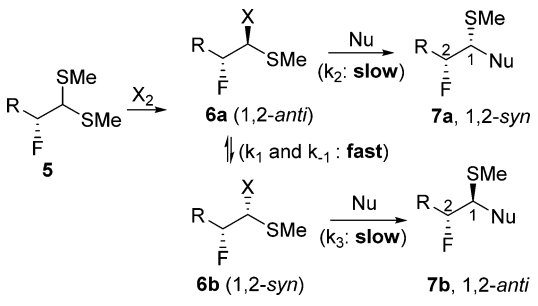
dithioacetals (R^2 = OBn), with high 1,2-*syn* selectivity.[16,17] These acyclic 1,2-*syn*-thioaminals undergo two distinct and stereoselective intramolecular cyclizations. Displacement of the activated thioether group with the C4-hydroxy results in an inversion of the C1 stereocenter and leads to D-1′,2′-*trans*-NAs **3** (O4′−C1 cyclization). Alternatively, displacement of a C4 leaving group by the thioether inverts the C4 stereocenter while maintaining the stereochemistry of the thioaminal providing L-1′,2′-*cis*-4-thionucleosides **4** (S1′−C4 cyclization).

In this current work, we report the applicability of this methodology to substrates bearing a C2′-fluorine (R^2 = F). This will provide a novel methodology to access C2′−F nucleoside analogues with an alkoxy group in C3′. In search of new antimetabolites that may serve as antiviral and/or anticancer agents, our laboratory is developing a series of novel nucleoside analogues. In particular, we are interested in those bearing an all-carbon stereogenic quaternary center at C3′ along with fluorine atoms in the C2′-position.[18,19] The acyclic approach is particularly well-suited for the efficient synthesis of these NAs.

RESULTS AND DISCUSSION

DFT and Experimental Model Study of Diastereoselective Dithioacetal Substitution. A model substrate was examined to determine the stereoselective outcome of nucleobase additions to dithioacetals with a C2-stereogenic center containing a fluoride atom. Our proposed mechanism for this substitution first involves the activation of a dithioacetal (**5**) with a halogen (X_2) to generate interconverting halothioether intermediates (**6a** and **6b**)[20] that subsequently react with the silylated nucleobase to generate 1,2-*syn*- and 1,2-*anti*-thioaminals **7a** and **7b** (Scheme 3). If the substitution steps (k_2 and k_3) are significantly slower than the epimerization (k_1),

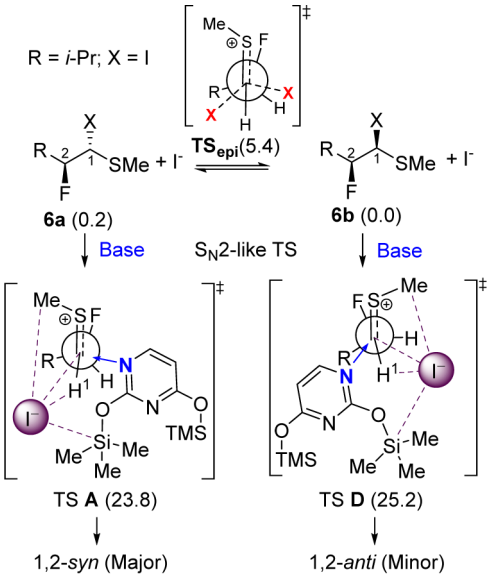
Scheme 3. Proposed Curtin−Hammett Scenario for the Substitution of Halothioethers Formed by Activation of Dithioacetal 5



the stereochemical outcome of the substitution reaction is dependent on the difference in free energy between the preferred transition states leading to the 1,2-*syn* and 1,2-*anti* products, as stated by the Curtin−Hammett principle.[21,22]

Highlights of the Computational Model Study. Substitution of halothioethers was examined by DFT calculations to determine the Gibbs free energies of the key transition states of our mechanistic hypothesis. Quantum mechanical calculations were done in Gaussian 09.[23] Geometry optimizations were performed with M06-2X[24,25] density functional using the 6-311+G** basis set in conjunction with the LANLDZpd[26,27] effective core potential. Frequency calculations were done on all optimized geometries to allow characterizations of minima (no imaginary frequencies) or transition structures (one imaginary frequency). The effect of the solvent was calculated with the polarizable continuum solvation model.[28] Free energy corrections were performed using Truhlar's quasiharmonic approximation.[29−31] The energy barrier for the epimerization of **6a**,**b** suggests a rapid equilibration between the *syn*- and *anti*-iodothioethers (TS_{epi} at 5.4 kcal/mol, Scheme 4). The substitution of these

Scheme 4. Lowest 1,2-*syn* (TS A), 1,2-*anti* (TS D), and Epimerization Transition Structures at the Origin of the 1,2-*syn* Inductions for Coupling of Silylated Uracil onto Dithioacetals in THF at 0 °C (Gibbs Free Energy in kcal/mol)



intermediates by the nucleobase (silylated uracil used to simplify calculations) was found to preferably proceed through an S_N2-like mechanism involving TS **A** and **D**, the 1,2-*syn* and 1,2-*anti* predictive transition structures, respectively. The Gibbs free energy difference between these TS corresponds to 1.4 kcal/mol in THF at 0 °C and thus an expected 13:1 diastereomeric ratio in favor of the 1,2-*syn*-thioaminal. This reaction pathway is similar to that previously reported for substitutions of C2-alkoxy dithioacetals.[20] It should be noted that all of the different low-energy C1−C2 and C2−C3 conformations were examined at the ground state and

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

transition state levels. Different leaving or attacking trajectories for iodide or the nucleophile were also screened. Furthermore, the S_N1 pathway was calculated to be prohibitively higher in energy.

Both transition structures **A** and **D** have a C1−C2 conformational preference orienting the C2-fluoro atom and thioether moiety in close proximity to one another (F−C−C−S dihedral angle 15° in TS **A** and 17° in TS **D**). This conformational preference, which is also present in TS_{epi} for the interconversion of halothioether species (**6a** and **6b**), could be responsible for the particular reactivity of dithioacetals bearing an electron-withdrawing group at C2.[20] Apart from potentially providing electrostatic stabilization from the high electron density on the C2 electronegative atom, this conformation allows for optimal σ(C2−R) and σ(C2−H) sigma donation to the π^*(S−C1) center at the transition state. This DFT study indicates that additions to C2-fluorodithioacetals should furnish synthetically useful 1,2-*syn* inductions.

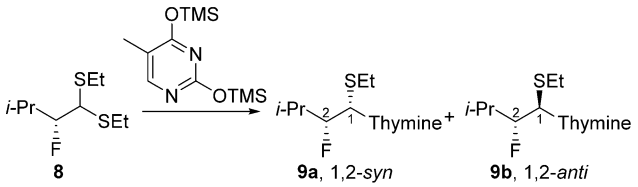
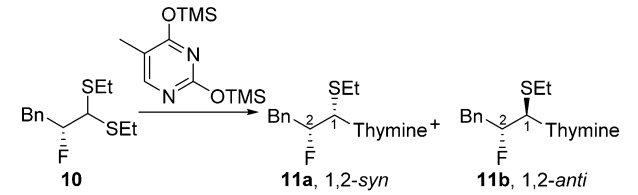
Experimental Model Study. Substitution of model dithioacetals **8** and **10** with silylated thymine was then investigated (Table 1). Diethyldithioacetal **8** bearing an isopropyl group gave a moderate 6:1 ratio in favor of the 1,2-*syn* diastereomer **9a** when coupled with silylated thymine in the presence of iodine at 0 °C (entry 1). This is consistent with the selectivity obtained from the DFT calculations assuming that the reaction is under kinetic control (Scheme 4). This assumption was further confirmed by the fact that the selectivities measured at different reaction temperatures (0, 25, and 70 °C) in THF (entries 1−3) follow Arrhenius' equation with the ratios remaining constant over time. However, a reaction mixture that reached completion at 25 °C in DCM (full conversion and ratio were determined from ^{1}H NMR of an aliquot of the reaction mixture) with a 4.2:1 ratio of thioaminals was then heated at 70 °C in DCM for several days and resulted in a decreased 1.5:1.0 ratio (entry 4). This indicates that the reaction could be reversible at higher temperatures in certain solvents, providing a thermodynamic distribution of products.

When done at 0 °C in DMSO instead of THF (entry 5 versus entry 1), the reaction occurred faster (16 h versus 48 h) with similar selectivity. Different activating agents were also examined for the substitution reaction. Addition to **8** provided comparable selectivity when activated with $Me_2S(SMe)BF_4$ (7:1, entries 6 and 7) compared to I_2. Treatment with $Hg(OAc)_2$ generated the corresponding acetate in situ, which was treated with TMSOTf and the nucleobase to provide the 1,2-*syn* diastereomer with similar selectivity (6:1, entries 8 and 9). The initial formation of halothioether intermediates **6a,b** (Scheme 3) is supported by ^{1}H NMR studies. Upon addition of bromine to dithioacetal **8** in THF-d_8 at −20 °C, two new species that display characteristic chemical shifts corresponding to bromothioethers were rapidly formed in approximately a 1:1.4 ratio despite the 4:1 ratio of 1,2-*syn*- and 1,2-*anti*-thioaminals **9a** and **9b** obtained (entry 10). This supports the hypothesis that the substitution occurs through the proposed Curtin−Hammett scenario, as outlined in Scheme 3. With a secondary chain attached at C2 (dithioacetal **10**), the 1,2-*syn* induction dropped significantly (2:1, Table 1, entry 11). This model study demonstrates that nucleobase addition onto C2-fluorodithioacetals bearing a substituent in the C3-position provides useful 1,2-*syn* inductions.

Additions to C2-Fluoro- and C3-Alkoxydithioacetals. With the encouraging 1,2-*syn* induction observed for model substrate **8**, nucleobase coupling onto more complex dithioacetals was investigated. The results with two acyclic dithioacetal scaffolds (2,3-*syn*-**12** and 2,3-*anti*-**14**) are presented in Table 2. As previously observed with polyoxygenated dithioacetals,[20] 2,3-*syn*-dithioacteal **12** provided high 1,2-*syn* dr (16:1) when coupled with silylated thymine in THF (Table 2, entry 1). An important decrease in selectivity (2:1) was measured with 2,3-*anti*-dithioacetal **14** (entry 5, Table 2).

The selectivity measured at different reaction temperatures suggests that the nucleobase addition is under kinetic control at room temperature (entries 1−3). Nucleobase addition in THF was not done at 0 °C as the model substrate showed incomplete conversion at this temperature (Table 1, entry 1). A lower selectivity in DCM versus THF was obtained (Table 2, entries 1 and 2) with a reversal of selectivity at 70 °C (entries 2 and 3). This may be caused by an equilibration in DCM allowing more of the thermodynamic 1,2-*anti* product to be formed. This substitution reaction could be performed at 0 °C in DMSO instead of 25 °C in THF (entries 1 and 4 and entries 5 and 6) with a slight increase in selectivity. Different activating agents were examined to perform the substitution reaction with

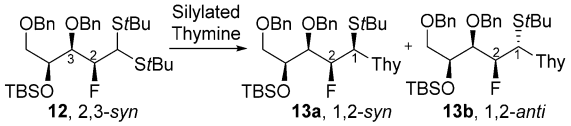
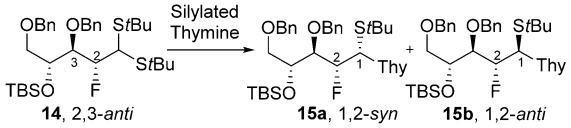
Table 1. Nucleobase Coupling on Model Substrates

Entry	Conditions	T	Ratio (**a**:**b**)[a]	Yield (%)
	 **8**		**9a**, 1,2-*syn*	**9b**, 1,2-*anti*
1	I_2, 48h, THF	0 °C	6.3:1	37[b]
2	I_2, 48h, THF	25 °C	5.9 :1	82
3	I_2, 24h, THF	70 °C	4.0:1	71
4	I_2, 24h, DCM	25 °C	4.2:1[c]	
	+ 6 days	70 °C	1.5:1	80
5	I_2, 16h, DMSO	0 °C	8:1	91
6	$Me_2S(SMe)BF_4$, 48h, THF	0 °C	7.1:1	57[b]
7	$Me_2S(SMe)BF_4$, 70h, THF	25 °C	6.7:1	91
8	$Hg(OAc)_2$, TMSOTf, 48h, THF	0 °C	5.6:1	63[b]
9	$Hg(OAc)_2$, TMSOTf, 48h, THF	25 °C	6.3:1	91
10	Br_2, 16h, THF	−20 °C	4:1	67
	 **10**		**11a**, 1,2-*syn*	**11b**, 1,2-*anti*
11	I_2, 116h, THF	25 °C	2:1	52[b]

[a]Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. [b]Starting material remaining in crude reaction mixture. [c]Full conversion by ^{1}H NMR.

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

Table 2. C2-Fluoro- and C3-Alkoxydithioacetals

Entry	Conditions	T	Ratio (**a**:**b**)[a]	Yield (%)
	 **12**, 2,3-*syn* **13a**, 1,2-*syn* **13b**, 1,2-*anti*			
1	I_2, 48h, THF	25 °C	16:1	70[b]
2	I_2, 48h, DCM	25 °C	12:1	62
3	I_2, 16h, DCM	70 °C	1:1.4	50
4	I_2, 16h, DMSO	0 °C	20:1	60[b]
	 **14**, 2,3-*anti* **15a**, 1,2-*syn* **15b**, 1,2-*anti*			
5	I_2, 48h, THF	25 °C	2:1	89
6	I_2, 48h, DMSO	0 °C	3:1	73
7	$Me_2S(SMe)BF_4$, 48h, THF	25 °C	4:1	57
8	$Hg(OAc)_2$, TMSOTf, 16h, THF	25 °C	5:1	52[c]
9	$Hg(OAc)_2$, TMSOTf, 16h, DCM	25 °C	6:1	49[c]

[a]Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. [b]Yield of 1,2-*syn* isomer. [c]Starting material remaining in crude mixture.

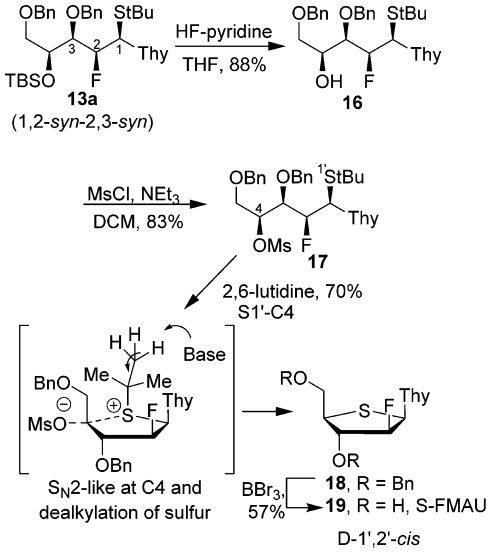
dithioacetal **14**. Addition to **14** at 25 °C provided an increase in selectivity for the 1,2-*syn* isomer **15a** with $Me_2S(SMe)BF_4$ and $Hg(OAc)_2$/TMSOTf activating agents (entries 7−9). The 1,2-*syn*/*anti* ratio for nucleobase coupling to 2,3-*anti*-dithioacetal **14** could therefore be improved with a variation of the activating agent and solvent from 2:1 to 6:1 (entries 5 and 9) albeit with lower yields. Thus, both 1,2-*syn*-thioaminal precursors with either a 2,3-*syn* or *anti* relationship could be obtained with good diastereoselectivity.

Synthesis of C2′−F and C3′-Alkoxy NAs. The thioaminal cyclization protocols previously developed by our group with C2-alkoxy intermediates[17] were next examined with the generated 1,2-*syn* C2−F substrates **13a** and **15a**.

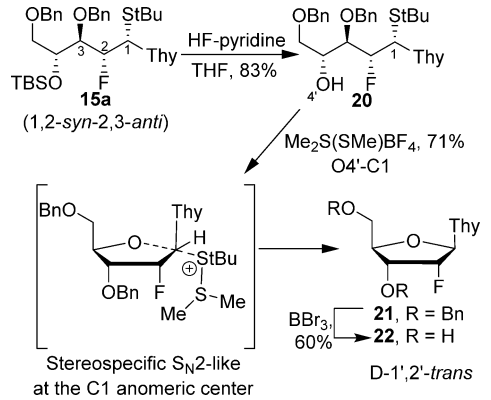
1′,2′-*cis* Nucleoside Synthesis. Deprotection of the C4−TBS of 1,2-*syn*-2,3-*syn*-thioaminal **13a** with subsequent mesylate installation provided thioaminal **17** (Scheme 5). A S1′ to C4 cyclization and dealkylation proceeded smoothly in 2,6-lutidine to access the protected D-1′,2′-*cis*-thiofuranoside **18**. The presence of the base (2,6-lutidine) is proposed to facilitate sulfur dealkylation.[32] The benzyl protecting groups were removed with BBr_3 to provide the unprotected D-1′,2′-*cis*-thiofuranoside S-FMAU.[5]

1′,2′-*trans* Nucleoside Synthesis. An O4′−C1 cyclization of the 1,2-*syn*-2,3-*anti* acyclic thioaminal **15a** was next examined to access D-1′,2′-*trans*-furanosides. Removal of the C4−TBS silyl protecting group using HF-pyridine in THF resulted in **20**. Activation of the −*S*tBu functionality at C1 using the sulfonium salt $Me_2S(SMe)BF_4$ resulted in the protected D-1′,2′-*trans*-furanoside **21** through an O4′ to C1 cyclization. The benzyl protecting groups were then removed to furnish nucleoside analogue **22** (Scheme 6).

Scheme 5. Synthesis of D-1′,2′-*cis*-Thiofuranoside S-FMAU through S1′−C4 Cyclization of Acyclic Thioaminal 13a



Scheme 6. Synthesis of D-1′,2′-*trans*-Furanoside 22 through O4′−C1 Cyclization of Acyclic Thioaminal 15a



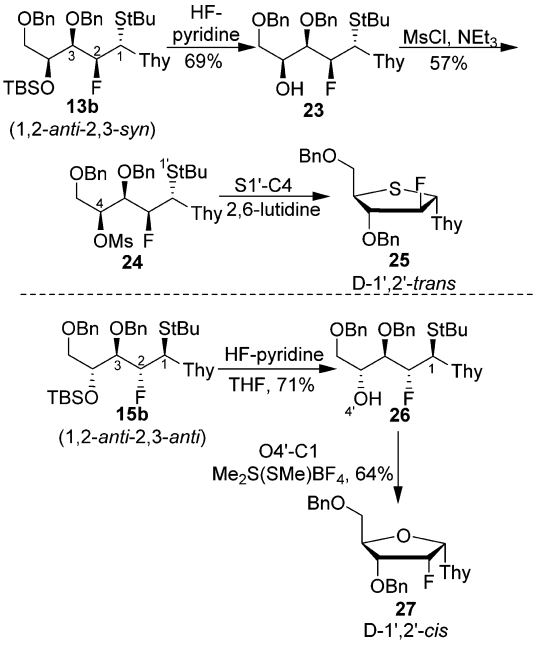
Therefore, we have demonstrated that the acyclic 1,2-*syn*-thioaminals bearing a C2-fluoro group can undergo the two modes of intramolecular S_N2-like cyclization (S1′−C4 and O4′−C1) providing two C2′−F nucleoside scaffolds that are difficult to access using other strategies (Scheme 1). In order to confirm that the S1′−C4 cyclization proceeds with retention of configuration at C1 and that the O4′−C1 cyclization results in C1 inversion, the minor 1,2-*anti*-thioaminals **13b** and **15b** were subjected to the cyclization conditions (Scheme 7).

Cyclization of 1,2-*anti*-thioaminal **24** provided only the D-1′,2′-*trans*-thionucleoside analogue **25** (>20:1). Silyl group deprotection of the minor 1,2-*anti*-2,3-*anti*-thioaminal **15b** followed by an O4′−C1 cyclization provided D-1′,2′-*cis*-furanoside **27**.

Additions to C2-Fluoro- and C3-Quaternary Center Dithioacetals. One of the advantages of the acyclic strategy presented herein is that various functionalities can be incorporated onto the acyclic thioaminal backbone, allowing for the formation of novel nucleoside analogues. We are interested in the synthesis and biological evaluation of scaffolds bearing a novel C3′ all-carbon quaternary center (Figure 1).[18] It is proposed that this stereogenic center may overcome some of the potential resistance mechanisms of current anticancer

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

Scheme 7. Cyclization of 1,2-*anti*-Thioaminals 13b and 15b



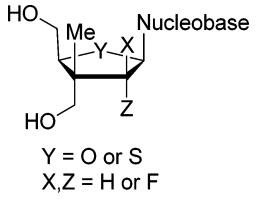


Figure 1. Novel nucleoside analogues bearing a C2′-fluoro and C3′-quaternary center.

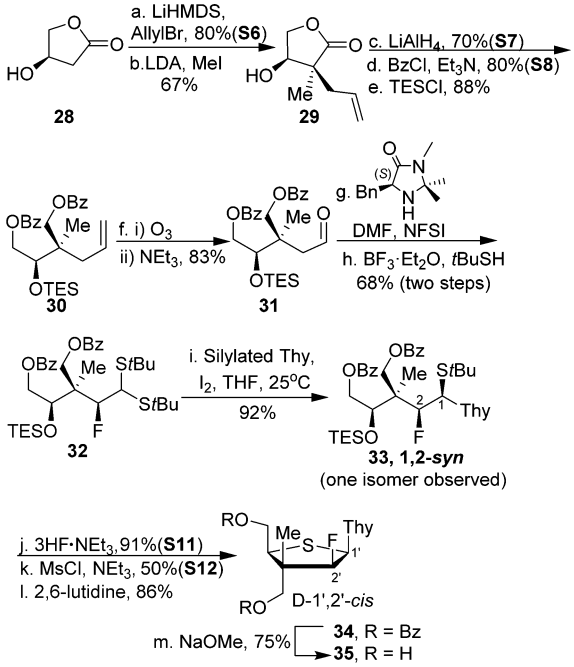
and antiviral agents. The acyclic approach is particularly well-suited for the efficient synthesis of such substrates.

The key precursors to generate 1′,2′-*cis*-thiofuranosides bearing a C3′-quaternary center and a C2′−F were obtained by allylation and subsequent methylation of (*R*)-*β*-hydroxy-*γ*-butyrolactone **28** (Scheme 8).

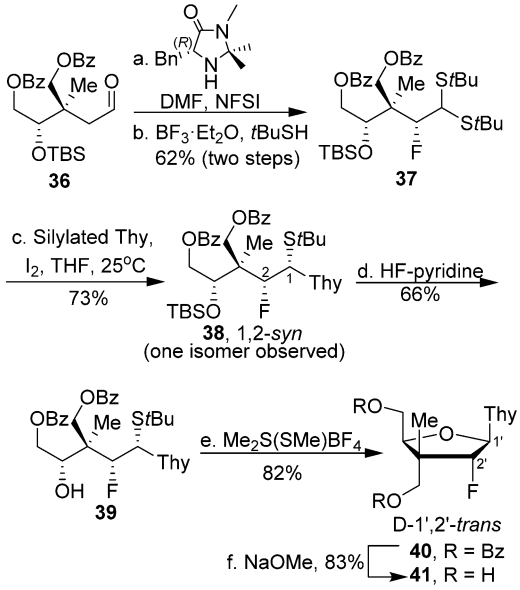
Reduction of the lactone **29** provided the acyclic triol, which was selectively benzoylated at the two primary alcohol positions and protected with a TES group on the secondary C4−OH, providing alkene **30**. This terminal olefin was then converted to the corresponding aldehyde **31** through ozonolysis. Selective introduction of the C2-fluoro group was accomplished using MacMillan's (*S*)-imidazolidinone catalyst[33−35] and NFSI to provide the fluorinated aldehyde. The ^{1}H NMR spectroscopic analysis of the unpurified C2−F aldehyde indicated a 17:1 diastereomeric ratio for the fluorination. Conversion into acyclic dithioacetal **32** was done using boron trifluoride diethyl etherate and *t*-butylthiol. Coupling of **32** with silylated thymine in the presence of iodine at 25 °C resulted in the selective formation of 1,2-*syn*-thioaminal **33**. Only one isomer could be detected by ^{1}H NMR. TES deprotection and mesylate installation followed by a S1′−C4 cyclization and debenzoylation provided the novel D-1′,2′-*cis*-thiofuranoside **35**.

Formation of D-1′,2′-*trans*-furanosides was accomplished using a similar strategy to access acyclic aldehyde **36** starting from (*S*)-*β*-hydroxy-*γ*-butyrolactone (Scheme 9). Interestingly, selective introduction (dr 17:1) of the C2-fluoro group was accomplished with the *R*-enantiomer of the imidazolidinone

Scheme 8. Synthesis of Novel D-1′,2′-*cis*-Thiofuranosides through a S1′−C4 Cyclization



Scheme 9. Synthesis of Novel D-1′,2′-*trans*-Furanosides through an O4′−C1 Cyclization



catalyst and NFSI to provide the C2−F aldehyde, which was converted into acyclic dithioacetal **37**. Coupling with silylated thymine in the presence of iodine resulted in the selective formation of 1,2-*syn*-thioaminal **38**. TBS deprotection followed by an O4′−C1 cyclization and debenzoylation provided the novel D-1′,2′-*trans*-furanoside **41**.

It was envisioned that the C4-deprotected 1,2-*syn*-thioaminal **39** could also be used to synthesize 1′,2′-*cis*-thiofuranosides of the L-series. The importance of L-analogues is highlighted by their antiviral activity and reduced cytotoxicity compared to that of their D-enantiomers.[36,37] The synthesis of novel L-thiofuranosides was thus accomplished through installation of a mesylate at C4 of acyclic thioaminal **39** followed by S1′−C4

DOI: 10.1021/acs.joc.6b01845
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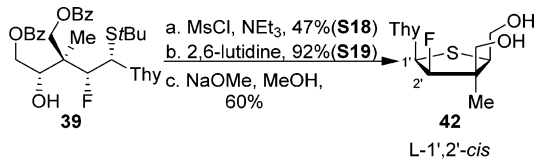
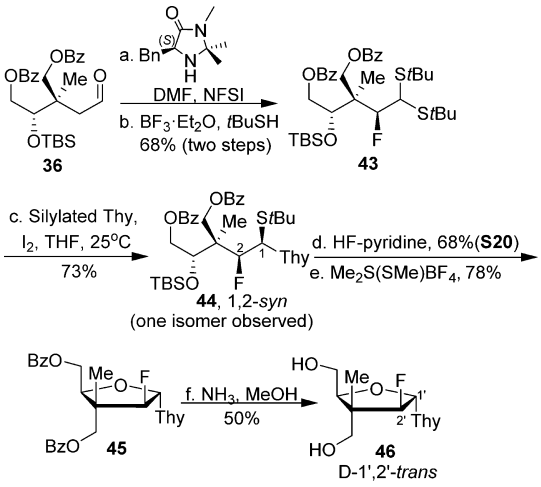
cyclization in the presence of 2,6-lutidine and debenzoylation (Scheme 10).

Scheme 10. Synthesis of Novel L-1′,2′-*cis*-Thiofuranosides through S1′−C4 Cyclization



When the (*S*)-imidazolidinone catalyst was used for the fluorination of aldehyde **36** (Scheme 11) as opposed to the

Scheme 11. Synthesis of Novel D-1′,2′-*trans*-Furanosides through an O4′−C1 Cyclization

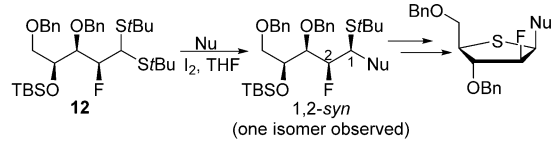
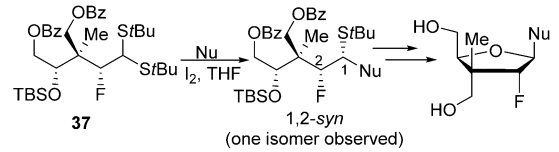
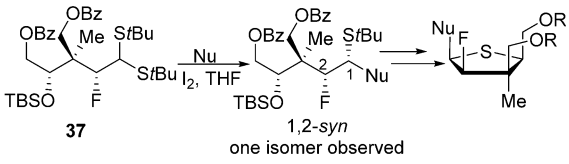


(*R*)-imidazolidinone (Scheme 9), the fluorine could be introduced with the opposite stereochemistry (dr 17:1) and converted to dithioacetal **43**. Nucleobase coupling provided the 1,2-*syn* thioaminal **44** in good yield and selectivity. Removal of the C4−TBS protecting group, O4′−C1 cyclization, and debenzoylation provided the *α*-1′,2′-*trans*-furanoside **46**. Interest in this particular series stems from a potential dual-face activity of such scaffolds.[18]

Preliminary Studies with Different Nucleobases. Although the acyclic approach was optimized with thymine, the synthesis of nucleoside analogues has also been examined with other nucleobases. Preliminary unoptimized studies demonstrate that 6-Cl-purine can be diastereoselectively (20:1) added to dithioacetal **12**, providing acyclic thioaminal **47** in modest yield (Table 3, entry 1). S1′−C4 cyclization of the C4−Ms substrate provided the D-1′,2′-*cis* nucleoside analogue **48**. Uracil, cytosine, and adenine derivatives were coupled to dithioacetal **37**, providing excellent diastereoselectively (20:1) and yields for the 1′,2′-*syn*-thioaminals **49**, **51**, and **55** (entries 2−6). These substrates could be employed in the two modes of S_N2-like cyclization, providing scaffolds **50**−**56**.

These novel nucleoside analogues bearing a C2′−F and a C3′ all-carbon quaternary center as well as their prodrugs are currently being tested as potential anticancer and antiviral agents.

Table 3. Acyclic Approach for the Synthesis of Nucleosides Bearing Different Nucleobases

Entry	Nucleobase	Thioaminal Formation Yield	Cyclization Yield	Nucleoside Analogue
				
		12	1,2-*syn* (one isomer observed)	
1	6-Cl-purine	**47**, 44%	45%	**48**
				
		37	1,2-*syn* (one isomer observed)	
2	Uracil(TMS)$_2$	**49**, 86%	73%	**50**
3	N^4-BzCytosine(TMS)$_2$	**51**, 81%	48%	**52**
				
		37	1,2-*syn* one isomer observed	
4[a]	Uracil(TMS)$_2$	**49**, 86%	91%	**53** (R=H)
5[a]	N^4-BzCytosine(TMS)$_2$	**51**, 81%	57%	**54** (R=Bz)
6	6-Cl-purine	**55**, 84%	40%	**56** (R=Bz)

[a]Nucleobase coupling conditions repeated.

CONCLUSIONS

Nucleobase coupling onto acyclic dithioacetals bearing a C2−F maintains preference for 1,2-*syn* stereocontrol. The stereoselective silylated nucleobase addition is proposed to occur through an S_N2-like mechanism where the C2−F and *S*-alkyl moiety are in close proximity to one another in both the major TS **A** (1,2-*syn*) and minor TS **D** (1,2-*anti*). Access to two NA scaffolds that are difficult to synthesize using standard approaches, namely, 1′,2′-*trans*-furanosides and 1′,2′-*cis*-thiofuranosides bearing a fluorine in the C2′-position is possible using our acyclic strategy. The acyclic methodology is well-suited to access a novel series of substrates in which high diastereoselective fluorination high 1,2-*syn* control for thioaminal formation, and efficient intramolecular S_N2-like cyclization provides NAs with a C2′−F and a C3′ all-carbon quaternary center that are being investigated as potential antimetabolites.

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. All anhydrous solvents were dried with 4 Å molecular sieves prior to use. The 4 Å molecular sieves (1−2 mm beads) were activated by being heated at 180 °C for 48 h under vacuum prior to being added to new bottles of solvent purged with argon. Commercially available reagents were used as received. Flash chromatography was performed on silica gel 60 (0.040−0.063 mm) using forced flow (flash chromatography) of the indicated solvent system 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

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

ammonium molybdate or potassium permanganate solutions. ^{1}H NMR spectra were recorded at room temperature on a 500 MHz NMR spectrometer. The data are reported as follows: chemical shift in parts per million referenced to residual solvent ($CDCl_3$ δ 7.26 ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, td = triplet of doublets, m = multiplet, app = apparent), coupling constants (hertz), and integration. The large J values (greater than 18 Hz) result from ^{1}H−F coupling. ^{13}C NMR spectra were recorded at room temperature using 125 MHz. The data are reported as follows: chemical shift in parts per million referenced to residual solvent ($CDCl_3$ δ 77.16 ppm). The large J values (greater than 18 Hz) result from ^{13}C−F coupling. Infrared spectra were recorded on a Fourier transform infrared spectrophotometer on a NaCl support, and signals are reported in cm^{-1}. Mass spectra were recorded through electrospray ionization positive ion mode. A Q exactive mass analyzer was used for HRMS measurements. Optical rotations were measured at room temperature from the sodium D line (589 nm) using $CDCl_3$ 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.

Preparation of Silylated Nucleobases.[38] To a suspension of the nucleobase in HMDS (2.7 equiv) under inert atmosphere was added $(NH_4)_2SO_4$ (0.1 equiv). The reaction mixture was refluxed at 180 °C until a clear solution was obtained (typically 3 h). Upon cooling to 25 °C, the solution was placed under high vacuum for ∼1 h to remove excess HMDS. A solution of the silylated nucleobase was made in the corresponding solvent (0.60−0.90 M).

Compounds from Table 1: *(2-Fluoro-3-methylbutane-1,1-diyl)bis(ethylsulfane) (**8**).* Isovaleraldehyde (1.0 mL, 9.3 mmol, 1.0 equiv) was added to a solution of (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt[39] (0.64 g, 1.9 mmol, 0.20 equiv) and NFSI (4.4 g, 14.0 mmol, 1.5 equiv) in THF/*i*PrOH(10%) (31.0 mL, 0.30 M) at −20 °C. The reaction mixture was stirred for 16 h at 0 °C. To verify that the reaction was complete, an aliquot was diluted with ether, filtered through a pad of silica gel, quenched with Me_2S, washed with a saturated solution of $NaHCO_3$, extracted with Et_2O, and dried with $MgSO_4$. Due to the volatility of the C2−F aldehyde, the diethyl ether was removed by a stream of air. Directly to the reaction mixture at 0 °C were added ethanethiol (2.8 mL, 37.3 mmol, 4.0 equiv) and concd HCl (6.0 mL, 74.6 mmol, 8.0 equiv). The reaction was stirred for 72 h at 25 °C followed by addition of NEt_3 (5 mL) and dilution with Et_2O (40 mL). A saturated solution (40 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 95:5) provided **8** as a colorless oil (1.1 g, 54%): R_f = 0.50 (hexanes/EtOAc, 95:5); $C_9H_{19}FS_2$; MW = 210.3756 g/mol; IR (neat) ν_{max} 2965, 2928, 2873 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (ddd, J = 47.2, 6.2, 5.4 Hz, 1H), 3.93 (dd, J = 22.6, 5.2 Hz, 1H), 2.82−2.65 (m, 4H), 2.35−2.23 (m, 1H), 1.27 (t, J = 7.4 Hz, 3H), 1.27 (t, J = 7.4 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 101.1 (d, J = 180.8 Hz), 52.8 (d, J = 22.2 Hz), 30.7 (d, J = 20.4 Hz), 25.0 (d, J = 2.5 Hz), 24.8 (d, J = 1.1 Hz), 19.0 (d, J = 6.7 Hz), 16.9 (d, J = 4.9 Hz), 14.59, 14.57 ppm; HRMS calcd for $C_9H_{19}FS_2Na$ [M + Na$^+$] 233.0804, found 233.0797 (−3.3 ppm). Since we were only interested in the diastereoselectivity for the coupling of the nucleobase to the dithioacetal, the enantioselectivity for introduction of the fluorine was not determined.

*(2-Fluoro-3-phenylpropane-1,1-diyl)bis(ethylsulfane) (**10**).* Hydrocinnamaldehyde (0.30 mL, 2.3 mmol, 1.0 equiv) was added to a solution of (*R*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one dichloroacetic acid salt[39] (0.16 g, 0.45 mmol, 0.20 equiv) and NFSI (1.1 g, 3.4 mmol, 1.5 equiv) in THF/*i*PrOH(10%) (7.0 mL, 0.30 M) at −20 °C. The reaction mixture was stirred for 16 h at 0 °C. To verify that the reaction was complete, an aliquot was diluted with ether, filtered through a pad of silica gel, quenched with Me_2S, washed with a saturated solution of $NaHCO_3$, extracted with Et_2O, and dried with $MgSO_4$. Due to the volatility of the C2−F aldehyde, the diethyl ether was removed by a stream of air. Directly to the reaction mixture at 0 °C were added ethanethiol (0.67 mL, 9.1 mmol, 4.0 equiv) and concd HCl (1.5 mL, 18.2 mmol, 8.0 equiv). The reaction was stirred for 16 h at 25 °C followed by addition of NEt_3 (2 mL) and dilution with Et_2O (10 mL). A saturated solution (10 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 95:5) provided **10** as a colorless oil (0.19 g, 32%): R_f = 0.32 (hexanes/EtOAc, 95:5); $C_{13}H_{19}FS_2$; MW = 258.4184 g/mol; IR (neat) ν_{max} 2963, 2926, 2869 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 4.99−4.85 (m, 1H), 3.92 (dd, J = 18.3, 4.4 Hz, 1H), 3.22 (ddd, J = 20.4, 14.1, 5.5 Hz, 2H), 2.83−2.69 (m, 4H), 1.33−1.26 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9 (d, J = 3.6 Hz), 129.6, 128.7, 126.9, 96.8 (d, J = 181.9 Hz), 53.8 (d, J = 21.8 Hz), 38.8 (d, J = 21.5 Hz), 25.63, 25.61, 14.64, 14.61 ppm; HRMS calcd for $C_{13}H_{19}FS_2Na$ [M + Na$^+$] 281.0804, found 281.0802 (−0.73 ppm). Since we were only interested in the diastereoselectivity for the coupling of the nucleobase to the dithioacetal, the enantioselectivity for introduction of the fluorine was not determined.

General Procedure A: To a solution of the corresponding C2−F dithioacetal in anhydrous solvent at 0 °C were added silylated nucleobase and the activating agent. The reaction mixture was stirred until complete by TLC. In certain cases, additional silylated thymine and activating agent were added in order for the reaction to go to completion. A saturated solution (1 mL) of $Na_2S_2O_3$ (with I_2 or Br_2) or $NaHCO_3$ (with $Hg(OAc)_2$/TMSOTf or $Me_2S(SMe)BF_4$) was added, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo.

*1-(1-(Ethylthio)-2-fluoro-3-methylbutyl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**9a** and **9b**).* Following general procedure A, silylated thymine (0.90 mL, 0.63 mmol, 3.0 equiv of a 0.71 M solution in DCM) and Br_2 (22 μL, 0.42 mmol, 2.0 equiv) were added to a solution of **8** (44 mg, 0.21 mmol) in anhydrous THF (2.0 mL, 0.10 M) and stirred at −20 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 3.5:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) did not allow separation of the diastereomers and provided a mixture of **9a** and **9b** (39 mg, 67%) as a white foam: R_f = 0.30 (hexanes/EtOAc, 70:30); $C_{12}H_{19}FN_2O_2S$; MW = 274.3549 g/mol; IR (neat) ν_{max} 3183, 2967, 1686 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (s, 1H, isomer **a**), 8.87 (s, 1H, isomer **b**), 7.68 (s, 1H, isomer **a**), 7.51 (s, 1H, isomer **b**), 6.09−5.94 (m, 2H, isomers **a** and **b**), 4.38 (ddd, J = 46.9, 7.6, 3.9 Hz, 1H, isomer **b**), 4.23 (ddd, J = 48.7, 9.4, 1.6 Hz, 1H, isomer **a**), 2.66−2.54 (m, 2H, isomer **b**), 2.51 (q, J = 7.4 Hz, 2H, isomer **a**), 2.20−2.08 (m, 1H, isomer **a**), 1.96 (s, 6H, isomers **a** and **b**), 1.90−1.78 (m, 1H, isomer **b**), 1.28 (t, J = 7.4 Hz, 3H, isomer **a**), 1.28 (t, J = 7.3 Hz, 3H, isomer **b**), 1.06−0.99 (m, 12H, isomers **a** and **b**) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7 (isomer **a**), 163.6 (isomer **b**), 151.5 (isomer **b**), 151.1 (isomer **a**), 138.0 (d, J = 5.0 Hz, isomer **a**), 137.8 (d, J = 6.6 Hz, isomer **b**), 111.9 (isomer **b**), 111.3 (isomer **a**), 101.0 (d, J = 180.6 Hz, isomer **a**), 99.1 (d, J = 52.8 Hz, isomer **b**), 61.1 (d, J = 19.3 Hz, isomer **a**), 59.3 (d, J = 22.0 Hz, isomer **b**), 30.9 (d, J = 19.1 Hz, isomer **a**), 30.3 (d, J = 19.6 Hz, isomer **b**), 25.2 (isomer **b**), 24.9 (isomer **a**), 18.5 (d, J = 4.8 Hz, isomer **a**), 18.4 (d, J = 10.1 Hz, isomer **b**), 17.8 (d, J = 8.6 Hz, isomer **a**), 17.5 (d, J = 6.5 Hz, isomer **b**), 14.7 (isomer **b**), 14.6 (isomer **a**), 12.83 (isomer **b**), 12.76 (isomer **a**) ppm; HRMS calcd for $C_{12}H_{19}FN_2O_2SNa$ [M + Na$^+$] 297.1043, found 297.1047 (1.07 ppm).

*1-(1-(Ethylthio)-2-fluoro-3-phenylpropyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**11a** and **11b**).* Following general procedure A, silylated thymine (0.70 mL, 0.45 mmol, 3.0 equiv of a 0.71 M solution in DCM) and I_2 (76 mg, 0.30 mmol, 2.0 equiv) were added to a solution of **10** (39 mg, 0.15 mmol) in anhydrous THF (1.5 mL, 0.10 M) and stirred at 25 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 2.3:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) did not allow separation of the diastereomers and provided a mixture of **11a** and **11b** (25 mg, 52%) as a white foam: R_f = 0.19 (hexanes/EtOAc, 70:30); $C_{16}H_{19}FN_2O_2S$; MW = 322.3977

DOI: 10.1021/acs.joc.6b01845
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g/mol; IR (neat) ν_{max} 3183, 3027, 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H, isomer **b**), 8.50 (s, 1H, isomer **a**), 7.61 (s, 1H, isomer **a**), 7.48 (s, 1H, isomer **b**), 7.33−7.17 (m, 10H, isomers **a** and **b**), 5.94 (dd, J = 24.0, 4.0 Hz, 1H, isomer **b**), 5.81 (dd, J = 29.2, 1.9 Hz, 1H, isomer **a**), 4.96−4.80 (m, 2H, isomers **a** and **b**), 3.24 (td, J = 13.9, 8.1 Hz, 1H, isomer **a**), 3.09−2.95 (m, 2H, isomers **a** and **b**), 2.91−2.79 (m, 1H, isomer **b**), 2.59−2.46 (m, 4H, isomers **a** and **b**), 1.93 (s, 3H, isomer **b**), 1.90 (s, 3H, isomer **a**), 1.27 (t, J = 7.2 Hz, 3H, isomer **b**), 1.26 (t, J = 7.3 Hz, 3H, isomer **a**) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5 (isomer **a**), 163.4 (isomer **b**), 151.4 (isomer **b**), 150.9 (isomer **a**), 137.7 (d, J = 4.8 Hz, isomer **a**), 137.4 (d, J = 4.6 Hz, isomer **b**), 135.4 (d, J = 1.6 Hz, isomer **b**), 135.3 (d, J = 6.0 Hz, isomer **a**), 129.4 (isomer **b**), 129.2 (isomer **a**), 128.9 (isomer **a**), 128.8 (isomer **b**), 127.4 (isomer **a**), 127.3 (isomer **b**), 112.0 (isomer **b**), 111.5 (isomer **a**), 96.9 (d, J = 181.5 Hz, isomer **a**), 95.1 (d, J = 183.0 Hz, isomer **b**), 62.3 (d, J = 19.7 Hz, isomer **a**), 61.1 (d, J = 17.1 Hz, isomer **b**), 39.4 (d, J = 21.3 Hz, isomer **a**), 38.8 (d, J = 21.0 Hz, isomer **b**), 25.4 (isomer **b**), 25.1 (isomer **a**), 14.7 (isomers **a** and **b**), 12.8 (isomer **b**), 12.7 (isomer **a**) ppm; HRMS calcd for $C_{16}H_{19}FN_2O_2SNa$ [M + Na^+] 345.1043, found 345.1045 (0.47 ppm).

Compounds from Table 2: *Synthesis of Dithioacetal* ***12****. (−)-(3S,4R,5S)-4-(Benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrofuran-2-ol (****S1****).* To a solution of the known glycal[40−42] derived from L-xylose (1.75 g, 5.9 mmol, 1.0 equiv) in 10:1 DMF/H_2O (30 mL, 0.18 M) was added Selectfluor (3.1 g, 8.8 mmol, 1.5 equiv). The reaction mixture was stirred at 25 °C for 16 h and concentrated. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided the C2-fluorinated lactol **S1** (0.77 g, 39%): R_f = 0.27 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ −5 (c 0.9, $CDCl_3$); $C_{19}H_{21}FO_4$; MW = 332.3714 g/mol; IR (neat) ν_{max} 3419, 2920, 2861 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.24 (m, 20H), 5.56−5.48 (m, 1H), 5.30 (appt, J = 12.8 Hz, 1H), 4.97 (dd, J = 52.3, 2.6 Hz, 1H), 4.93 (dt, J = 52.0, 3.2 Hz, 1H), 4.74−4.47 (m, 7H), 4.41 (dd, J = 9.6, 4.3 Hz, 1H), 4.27 (tdd, J = 18.0, 5.5, 3.0 Hz, 2H), 4.09 (d, J = 11.9 Hz, 1H), 3.78−3.64 (m, 4H), 3.23 (d, J = 5.5 Hz, 1H) ppm *OH signals missing possibly due to exchange in* $CDCl_3$; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 137.51, 137.48, 137.2, 128.8, 128.71, 128.70, 128.5, 128.4, 128.20, 128.16, 128.1, 128.0, 127.9, 127.83, 127.81, 101.2 (d, J = 34.2 Hz), 99.1 (d, J = 185.5 Hz), 96.0 (d, J = 17.3 Hz), 93.9 (d, J = 190.2 Hz), 81.2 (d, J = 24.6 Hz), 80.7, 80.5, 80.2 (d, J = 3.2 Hz), 74.1, 73.8, 73.3, 73.0, 68.52, 68.49 ppm; HRMS calcd for $C_{19}H_{21}FO_4Na$ [M + Na^+] 355.1316, found 355.1320 (1.05 ppm).

*(+)-(2S,3R,4R)-1,3-Bis(benzyloxy)-4-fluorohex-5-en-2-ol (****S2****).* To a solution of dry methyltriphenylphosphonium bromide (2.5 g, 6.9 mmol, 3.0 equiv, dried with benzene and left 16 h under high vacuum) in anhydrous THF (13.0 mL, 0.55 M) at 0 °C was added potassium bis(trimethylsilyl)amide (14.0 mL, 6.9 mmol, 3.0 equiv of a 0.5 M solution in toluene). The reaction mixture was stirred at 25 °C for 2 h. Upon cooling to 0 °C, **S1** (0.77 g, 2.3 mmol, 1.0 equiv) as a solution in anhydrous THF (8.0 mL, 0.30 M) was added and stirred for 3 h at 0 °C. Silica gel (1.2 g) was added, and the reaction was concentrated to remove THF. The crude mixture was dissolved in diethyl ether (30.0 mL) and passed through a pad of silica gel. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **S2** (0.58 g, 76%) as a colorless oil: R_f = 0.34 (hexanes/EtOAc, 80:20); $[\alpha]_D^{25}$ +23 (c 0.9, $CDCl_3$); $C_{20}H_{23}FO_3$; MW = 330.3994 g/mol; IR (neat) ν_{max} 3392, 3027, 2850 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 6.02−5.91 (m, 1H), 5.50−5.45 (m, 1H), 5.36 (d, J = 10.7 Hz, 1H), 5.15 (appdt, J = 48.4, 6.6 Hz, 1H), 4.84 (d, J = 11.2 Hz, 1H), 4.57 (d, J = 11.3 Hz, 1H), 4.49 (appq, J = 11.9 Hz, 2H), 3.91−3.84 (m, 1H), 3.66 (ddd, J = 15.3, 6.6, 2.8 Hz, 1H), 3.56−3.44 (m, 2H), 2.28 (d, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 138.1, 133.2 (d, J = 18.9 Hz), 128.61, 128.57, 128.4, 128.1, 128.02, 127.98, 119.6 (d, J = 12.2 Hz), 94.7 (d, J = 171.8 Hz), 80.1 (d, J = 20.5 Hz), 75.0 (d, J = 2.7 Hz), 73.6, 71.2, 69.8 (d, J = 5.9 Hz) ppm; HRMS calcd for $C_{20}H_{23}FO_3Na$ [M + Na^+] 353.1523, found 353.1529 (1.55 ppm).

*(−)-(((2S,3R,4R)-1,3-Bis(benzyloxy)-4-fluorohex-5-en-2-yl)oxy)(tert-Butyl)dimethylsilane (****S3****).* To a solution of **S2** (1.6 g, 4.7 mmol, 1.0 equiv) in anhydrous DCM (10 mL, 0.50 M) at 0 °C were added 2,6-lutidine (1.4 mL, 11.8 mmol, 2.5 equiv) and TBSOTf (1.7 mL, 7.1 mmol, 1.5 equiv). The reaction was stirred for 5 h at 0 °C. A saturated solution (5 mL) of NH_4Cl was added, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 95:5) provided **S3** (1.74 g, 83%) as a colorless oil: R_f = 0.53 (hexanes/EtOAc, 95:5); $[\alpha]_D^{25}$ −11 (c 1.1, $CDCl_3$); $C_{26}H_{37}FO_3Si$; MW = 444.6624 g/mol; IR (neat) ν_{max} 2925, 2855 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.27 (m, 10H), 6.05−5.94 (m, 1H), 5.43−5.38 (m, 1H), 5.28 (d, J = 10.7 Hz, 1H), 5.25−5.12 (m, 1H), 4.70 (dd, J = 27.0, 11.7 Hz, 2H), 4.52 (apps, 2H), 4.05 (ddd, J = 6.5, 4.9, 3.4 Hz, 1H), 3.73 (dd, J = 10.1, 3.2 Hz, 1H), 3.59−3.53 (m, 1H), 3.49 (dt, J = 24.1, 4.4 Hz, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.5, 134.4 (d, J = 19.7 Hz), 128.5, 128.4, 128.1, 127.82, 127.79, 127.6, 117.8 (d, J = 12.2 Hz), 92.6 (d, J = 173.7 Hz), 81.8 (d, J = 18.5 Hz), 74.3 (d, J = 1.1 Hz), 73.5, 72.22 (d, J = 4.1 Hz), 72.16 (d, J = 3.2 Hz), 26.1, 18.3, −4.1, −4.7 ppm; HRMS calcd for $C_{26}H_{37}FO_3SiNa$ [M + Na^+] 467.2388, found 467.2396 (1.6 ppm).

*(−)-(((2S,3R,4S)-1,3-Bis(benzyloxy)-5,5-bis(tert-butylthio)-4-fluoropentan-2-yl)oxy)(tert-Butyl)dimethylsilane (****12****).* To a solution of **S3** (1.74 g, 3.9 mmol, 1.0 equiv) in DCM (150 mL, 0.026 M) at −78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 20 min). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (1.1 mL, 7.8 mmol, 2.0 equiv), the reaction was warmed to 25 °C for 30 min. A 1 N HCl solution (20 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. To the crude C2−F aldehyde in anhydrous DCM (40 mL, 0.10 M) at −60 °C was added *t*BuSH (1.8 mL, 15.7 mmol, 4.0 equiv) and $BF_3{\cdot}OEt_2$ (1.3 mL, 9.8 mmol, 2.5 equiv). The reaction was stirred at −60 °C for 5 h. NEt_3 (2.2 mL, 15.7 mmol, 4.0 equiv) was added, and stirring at −60 °C was maintained for 15 min. A saturated solution (10 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **12** (1.85 g, 78%) as a colorless oil: R_f = 0.48 (hexanes/EtOAc, 90:10); $[\alpha]_D^{25}$ −1.9 (c 1.3, $CDCl_3$); $C_{33}H_{53}FO_3S_2Si$; MW = 608.9874 g/mol; IR (neat) ν_{max} 2958, 2925, 2861 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.23 (m, 10H), 4.77−4.63 (m, 3H), 4.50 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.35 (dd, J = 8.5, 7.0 Hz, 1H), 4.20−4.11 (m, 2H), 3.80 (d, J = 10.4 Hz, 1H), 3.57−3.51 (m, 1H), 1.39 (s, 9H), 1.37 (s, 9H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 138.6, 128.44, 128.35, 127.8, 127.73, 127.69, 127.5, 92.0 (d, J = 187.5 Hz), 78.4 (d, J = 17.1 Hz), 73.5, 73.4, 72.7 (d, J = 7.0 Hz), 72.0, 47.4 (d, J = 24.6 Hz), 46.0, 45.5, 32.1 (d, J = 2.0 Hz), 31.9, 26.1, 18.4, −4.2, −4.4 ppm; HRMS calcd for $C_{33}H_{53}FO_3S_2SiNa$ [M + Na^+] 631.3082, found 631.3087 (0.91 ppm).

Synthesis of Dithioacetal ***14****. (+)-(2R,3R,4S)-1,3-Bis(benzyloxy)-4-fluorohex-5-en-2-ol (****S4****).* To a solution of dry methyltriphenylphosphonium bromide (1.6 g, 4.5 mmol, 3.0 equiv, dried with benzene and left 16 h under high vacuum) in anhydrous THF (8.0 mL, 0.55 M) at 0 °C was added potassium bis(trimethylsilyl)amide (9.0 mL, 4.5 mmol, 3.0 equiv of a 0.5 M solution in toluene). The reaction mixture was stirred at 25 °C for 2 h. Upon cooling to 0 °C, the starting lactol[43] derived from D-arabinose (0.50 g, 1.5 mmol, 1.0 equiv) as a solution in anhydrous THF (5.0 mL, 0.30 M) was added and stirred for 3 h at 0 °C. Silica gel (0.80 g) was added, and the reaction was concentrated to remove THF. The crude mixture was dissolved in diethyl ether (30.0 mL) and passed through a pad of silica gel. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **S4** (0.39 g, 78%) as a colorless oil: R_f = 0.59 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +58 (c 1.4, $CDCl_3$); $C_{20}H_{23}FO_3$; MW = 330.3932 g/mol; IR (neat) ν_{max} 3468, 2925, 2860 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.25 (m, 10H), 6.09 (dddd, J = 17.5, 13.4, 10.7, 6.9 Hz, 1H), 5.47 (ddd, J = 17.4, 2.5, 1.3 Hz, 1H), 5.39 (d, J = 10.7 Hz, 1H), 5.34−5.21 (m, 1H),

DOI: 10.1021/acs.joc.6b01845
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4.80 (d, J = 11.3 Hz, 1H), 4.56−4.48 (m, 3H), 3.84 (ddd, J = 14.1, 8.3, 2.7 Hz, 1H), 3.71 (ddd, J = 14.0, 7.1, 4.5 Hz, 1H), 3.67−3.63 (m, 1H), 3.60 (dd, J = 9.5, 5.6 Hz, 1H), 2.42 (d, J = 5.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 137.9, 132.3 (d, J = 19.9 Hz), 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 120.0 (d, J = 12.2 Hz), 95.1 (d, J = 168.6 Hz), 80.1 (d, J = 21.1 Hz), 74.3 (d, J = 2.6 Hz), 73.6, 70.7 (d, J = 1.4 Hz), 69.9 (d, J = 8.1 Hz) ppm; HRMS calcd for $C_{20}H_{23}FO_3Na$ [M + Na^+] 353.1523, found 353.1525 (0.54 ppm).

*(+)-(((2R,3R,4S)-1,3-Bis(benzyloxy)-4-fluorohex-5-en-2-yl)oxy)(tert-Butyl)dimethylsilane (**S5**).* To a solution of **S4** (0.80 g, 2.4 mmol, 1.0 equiv) in anhydrous DCM (5.0 mL, 0.50 M) at 0 °C were added 2,6-lutidine (0.70 mL, 6.0 mmol, 2.5 equiv) and TBSOTf (0.85 mL, 3.6 mmol, 1.5 equiv). The reaction was stirred for 3 h at 25 °C. A saturated solution (2 mL) of NH_4Cl was added, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **S5** (0.96 g, 89%) as a colorless oil: R_f = 0.25 (hexanes/EtOAc, 95:5); $[\alpha]_D^{25}$ +5.9 (c 1.1, $CDCl_3$); $C_{26}H_{37}FO_3Si$; MW = 444.6541 g/mol; IR (neat) ν_{max} 2954, 2929, 2857 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.23 (m, 10H), 6.08 (dddd, J = 17.1, 15.1, 10.8, 6.2 Hz, 1H), 5.50−5.44 (m, 1H), 5.38 (d, J = 10.8 Hz, 1H), 5.29−5.15 (m, 1H), 4.73 (d, J = 11.3 Hz, 1H), 4.65 (d, J = 11.3 Hz, 1H), 4.52 (apps, 2H), 3.96−3.91 (m, 1H), 3.85 (ddd, J = 12.9, 5.9, 4.4 Hz, 1H), 3.67 (dd, J = 9.5, 3.1 Hz, 1H), 3.59 (dd, J = 10.0, 5.1 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.4, 133.1 (d, J = 18.7 Hz), 128.44, 128.40, 128.1, 127.9, 127.72, 127.67, 119.2 (d, J = 12.3 Hz), 93.7 (d, J = 169.0 Hz), 81.4 (d, J = 22.7 Hz), 74.3 (d, J = 1.7 Hz), 73.4, 72.0 (d, J = 6.5 Hz), 71.8 (d, J = 2.0 Hz), 26.1, 18.3, −4.0, −4.7 ppm; HRMS calcd for $C_{26}H_{37}FO_3SiNa$ [M + Na^+] 467.2388, found 467.2383 (−1.1 ppm).

*(−)-(((2R,3R,4R)-1,3-Bis(benzyloxy)-5,5-bis(tert-butylthio)-4-fluoropentan-2-yl)oxy)(tert-Butyl)dimethylsilane (**14**).* To a solution of **S5** (0.37 g, 0.82 mmol, 1.0 equiv) in DCM (33.0 mL, 0.025 M) at −78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 15 min). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (0.23 mL, 1.6 mmol, 2.0 equiv), the reaction was warmed to 25 °C for 45 min. A 1 N HCl solution (20 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. To the crude C2−F aldehyde in anhydrous DCM (8.0 mL, 0.10 M) at −60 °C were added *t*BuSH (0.37 mL, 3.3 mmol, 4.0 equiv) and $BF_3{\cdot}OEt_2$ (0.26 mL, 2.1 mmol, 2.5 equiv). The reaction was stirred at −40 °C for 4 h. NEt_3 (0.46 mL, 3.3 mmol, 4.0 equiv) was added, and stirring at −40 °C was maintained for 15 min. A saturated solution (5 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 95:5) provided **14** (0.34 g, 68%) as a colorless oil: R_f = 0.43 (hexanes/EtOAc, 90:10); $[\alpha]_D^{25}$ −15 (c 1.0, $CDCl_3$); $C_{33}H_{53}FO_3S_2Si$; MW = 608.9860 g/mol; IR (neat) ν_{max} 2958, 2936, 2855 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.24 (m, 10H), 5.02 (dd, J = 45.8, 9.0 Hz, 1H), 4.96 (d, J = 11.5 Hz, 1H), 4.53 (appt, J = 11.0 Hz, 3H), 4.49−4.32 (m, 2H), 4.11 (dd, J = 9.0, 3.1 Hz, 1H), 3.70 (dd, J = 9.8, 5.5 Hz, 1H), 3.57−3.52 (m, 1H), 1.35 (s, 9H), 1.35 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.5, 128.41, 128.38, 127.8, 127.6, 127.5, 127.2, 95.3 (d, J = 177.4 Hz), 80.8 (d, J = 25.3 Hz), 73.5, 73.1, 72.1 (d, J = 5.8 Hz), 71.4, 47.3 (d, J = 20.2 Hz), 45.8, 44.0, 31.8, 31.6, 26.0, 18.3, −4.5, −4.6 ppm; HRMS calcd for $C_{33}H_{53}FO_3S_2SiNa$ [M + Na^+] 631.3082, found 631.3076 (−0.93 ppm).

*Synthesis of Thioaminals **13** and **15**. (+)-1-((1R,2S,3R,4S)-3,5-Bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**13a**) and (−)-1-((1S,2S,3R,4S)-3,5-Bis(benzyloxy)-4-((tert-butyldimethylsilyl)-oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**13b**).* Following general procedure A, silylated thymine (1.0 mL, 0.67 mmol, 3.0 equiv of a 0.70 M solution in THF) and I_2 (0.11 g, 0.45 mmol, 2.0 equiv) were added to a solution of **12** (0.14 g, 0.22 mmol, 1.0 equiv) in anhydrous THF (2.3 mL, 0.10 M) and stirred at 25 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 16:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **13a** (0.10 g, 70%) as a white foam: R_f = 0.28 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +46 (c 1.2, $CDCl_3$); $C_{34}H_{49}FN_2O_5SSi$; MW = 644.9184 g/mol; IR (neat) ν_{max} 3199, 2920, 2861, 1680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.44 (s, 1H), 7.38−7.26 (m, 10H), 6.18 (dd, J = 16.6, 5.9 Hz, 1H), 4.84 (appd, J = 46.5 Hz, 1H), 4.74 (d, J = 11.0 Hz, 1H), 4.61 (d, J = 11.1 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.41 (d, J = 12.0 Hz, 1H), 4.12−4.07 (m, 1H), 3.69 (dd, J = 9.8, 2.9 Hz, 1H), 3.59 (appd, J = 22.0 Hz, 1H), 3.48−3.41 (m, 1H), 1.89 (s, 3H), 1.32 (s, 9H), 0.82 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 150.2, 138.5, 138.2, 138.0, 128.5, 128.4, 128.2, 127.9, 127.7, 127.6, 111.6, 92.2 (d, J = 188.1 Hz), 78.1 (d, J = 16.3 Hz), 74.0, 73.4, 71.7, 70.9, 58.5 (d, J = 25.6 Hz), 45.3, 31.3, 26.0, 18.2, 12.7, −4.0, −4.8 ppm; HRMS calcd for $C_{34}H_{49}FN_2O_5SSiNa$ [M + Na^+] 667.3008, found 667.3027 (2.91 ppm).

Following general procedure A, silylated thymine (1.0 mL, 0.65 mmol, 3.0 equiv of a 0.74 M solution in DCM) and I_2 (0.12 g, 0.44 mmol, 2.0 equiv) were added to a solution of **12** (0.13 g, 0.22 mmol, 1.0 equiv) in anhydrous DCM (2.2 mL, 0.10 M) and stirred at 70 °C for 16 h. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:1.4 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **13a** (35 mg) and **13b** (35 mg) for a total of a 50% yield.

13b: R_f = 0.24 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ −45 (c 0.9, $CDCl_3$); $C_{34}H_{49}FN_2O_5SSi$; MW = 644.9184 g/mol; IR (neat) ν_{max} 3188, 2925, 2850, 1674 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.36 (s, 1H), 7.35−7.25 (m, 10H), 6.25 (dd, J = 17.2, 6.6 Hz, 1H), 4.88 (dd, J = 45.7, 6.5 Hz, 1H), 4.72 (d, J = 11.4 Hz, 1H), 4.55 (d, J = 11.3 Hz, 1H), 4.46 (apps, 2H), 4.24−4.20 (m, 1H), 3.83 (dd, J = 28.1, 5.3 Hz, 1H), 3.73 (appd, J = 10.3 Hz, 1H), 3.47−3.41 (m, 1H), 1.90 (s, 3H), 1.29 (s, 9H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 150.8, 138.5, 137.7, 137.5 (d, J = 2.3 Hz), 128.6, 128.4, 127.9, 127.7, 127.6, 127.4, 111.3, 91.1 (d, J = 187.9 Hz), 78.6 (d, J = 16.2 Hz), 77.4, 73.3, 71.9 (d, J = 6.3 Hz), 70.7, 58.0 (d, J = 20.5 Hz), 45.7, 31.1, 26.0, 18.2, 12.8, −4.2, −4.9 ppm; HRMS calcd for $C_{34}H_{49}FN_2O_5SSiNa$ [M + Na^+] 667.3008, found 667.3017 (1.46 ppm).

*(−)-1-((1S,2R,3R,4R)-3,5-Bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**15a**) and (+)-(1-((1R,2R,3R,4R)-3,5-Bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**15b**).* Following general procedure A, silylated thymine (0.90 mL, 0.62 mmol, 3.0 equiv of a 0.71 M solution in DCM) and I_2 (0.11 g, 0.41 mmol, 2.0 equiv) were added to a solution of **14** (0.13 g, 0.21 mmol) in anhydrous THF (2.0 mL, 0.10 M) and stirred at 25 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 2.4:1 mixture of 1,2-*syn* and *anti* diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **15a** (5 mg), a mix of **15a** and **15b** (88 mg) and **15b** (25 mg) for a total percent yield of 89% of white foams.

15a: R_f = 0.42 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ −22 (c 1.2, $CDCl_3$); $C_{34}H_{49}FN_2O_5SSi$; MW = 644.9122 g/mol; IR (neat) ν_{max} 3183, 3054, 2920, 1685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.63 (s, 1H), 7.40−7.23 (m, 10H), 6.39 (appd, J = 33.0 Hz, 1H), 5.00 (d, J = 11.7 Hz, 1H), 4.90 (dd, J = 47.8, 9.2 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.49 (appq, J = 11.9 Hz, 2H), 4.25 (appt, J = 6.0 Hz, 1H), 4.01 (dd, J = 9.2, 4.7 Hz, 1H), 3.67 (dd, J = 9.6, 6.5 Hz, 1H), 3.54−3.46 (m, 1H), 1.95 (s, 3H), 1.22 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 150.1, 138.7 (d, J = 3.3 Hz), 138.3, 138.1, 128.48, 128.46, 127.74, 127.71, 127.5, 126.8, 110.8, 95.4 (d, J = 178.5 Hz), 80.3 (d, J = 24.2 Hz), 73.53, 73.49, 71.4 (d, J = 4.4 Hz), 71.1, 59.2 (d, J = 17.3 Hz), 44.8, 31.1, 26.0, 18.3, 12.7,

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

−4.6, −4.7 ppm; HRMS calcd for $C_{34}H_{49}FN_2O_5SSiNa$ [M + Na^+] 667.3008, found 667.3021 (2.1 ppm).

15b: R_f = 0.44 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +27 (*c* 0.9, $CDCl_3$); $C_{34}H_{49}FN_2O_5SSi$; MW = 644.9122 g/mol; IR (neat) ν_{max} 3183, 3033, 2928, 1700, 1683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.50 (s, 1H), 7.35−7.23 (m, 10H), 6.28 (appd, *J* = 27.8 Hz, 1H), 5.00 (ddd, *J* = 7.0, 6.3, 1.6 Hz, 1H), 4.63 (d, *J* = 10.5 Hz, 1H), 4.54 (d, *J* = 10.4 Hz, 1H), 4.47 (apps, 2H), 4.24 (appq, *J* = 4.7 Hz, 1H), 3.75 (dd, *J* = 12.5, 7.0 Hz, 1H), 3.61 (dd, *J* = 9.9, 4.4 Hz, 1H), 3.57 (dd, *J* = 9.9, 4.9 Hz, 1H), 1.82 (s, 3H), 1.29 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 150.7, 139.0 (d, *J* = 5.9 Hz), 138.2, 137.9, 128.5, 128.4, 128.2, 127.9, 127.81, 127.75, 110.7, 95.5 (d, *J* = 180.4 Hz), 79.9 (d, *J* = 23.0 Hz), 74.6, 73.4, 71.3 (d, *J* = 5.4 Hz), 71.1 (d, *J* = 2.3 Hz), 56.7 (d, *J* = 18.0 Hz), 45.4, 31.2, 26.0, 18.3, 12.6, −4.2, −4.7 ppm; HRMS calcd for $C_{34}H_{49}FN_2O_5SSiNa$ [M + Na^+] 667.3008, found 667.3012 (0.57 ppm).

Synthesis of D-1′,2′-cis-Thiofuranoside ***19*** *(Scheme 5). (+)-1-((1R,2S,3R,4S)-3,5-Bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione* ***(16)****.* To a solution of **13a** (104 mg, 0.16 mmol, 1.0 equiv) in anhydrous THF (1.7 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.40 mL, 2 mL/mmol, ∼70% HF). The reaction was stirred for 16 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **16** (75.2 mg, 88%): R_f = 0.20 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +74 (*c* 1.3, $CDCl_3$); $C_{28}H_{35}FN_2O_5S$; MW = 530.6554 g/mol; IR (neat) ν_{max} 3425, 3188, 2958, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ8.72 (s, 1H), 7.67 (s, 1H), 7.38−7.24 (m, 10H), 6.17 (appd, *J* = 31.7 Hz, 1H), 5.00 (appdd, *J* = 50.1, 8.3 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 4.57 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.03 (apps, 1H), 3.94 (appt, *J* = 9.1 Hz, 1H), 3.62−3.55 (m, 1H), 3.42 (dd, *J* = 9.0, 5.8 Hz, 1H), 2.94 (s, 1H), 1.96 (s, 3H), 1.29 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 150.6, 138.2 (d, *J* = 2.5 Hz), 138.03, 137.98, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 111.1, 98.3 (d, *J* = 181.7 Hz), 77.9 (d, *J* = 16.7 Hz), 75.1 (d, *J* = 3.3 Hz), 73.5, 70.9, 69.4 (d, *J* = 7.3 Hz), 58.7 (d, *J* = 18.7 Hz), 45.0, 31.2, 12.7 ppm; HRMS calcd for $C_{28}H_{35}FN_2O_5SNa$ [M + Na^+] 553.2143, found 553.2149 (1.02 ppm).

(+)-(2S,3R,4S,5R)-1,3-Bis(benzyloxy)-5-(tert-butylthio)-4-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)pentan-2-yl methanesulfonate ***(17)****.* To a solution of **16** (75 mg, 0.14 mmol, 1.0 equiv) in anhydrous DCM (0.50 mL, 0.30 M) at 0 °C were added triethylamine (40 μL, 0.28 mmol, 2.0 equiv) and methanesulfonyl chloride (20 μL, 0.21 mmol, 1.5 equiv). The reaction was stirred for 5 h at 25 °C. A 1.0 N solution (0.50 mL) of HCl was added, and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **17** (75.9 mg, 83%): R_f = 0.15 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +64 (*c* 0.8, $CDCl_3$); $C_{29}H_{37}FN_2O_7S_2$; MW = 608.7404 g/mol; IR (neat) ν_{max} 3178, 3038, 2963, 1688 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.65 (s, 1H), 7.37−7.28 (m, 10H), 6.14 (appd, *J* = 28.1 Hz, 1H), 5.03 (apptd, *J* = 6.1, 3.5 Hz, 1H), 4.85 (appd, *J* = 50.2 Hz, 1H), 4.78 (d, *J* = 10.9 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.12 (ddd, *J* = 10.9, 5.5, 2.8 Hz, 1H), 3.89−3.82 (m, 2H), 3.14 (s, 3H), 1.95 (s, 3H), 1.34 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 150.3, 138.2, 137.6, 137.5, 128.7, 128.6, 128.4, 128.3, 128.1, 127.9, 111.1, 95.5 (d, *J* = 192.9 Hz), 77.1, 75.5, 73.7, 67.9, 58.5, 45.8, 38.7, 31.7, 31.3, 12.6 ppm; HRMS calcd for $C_{29}H_{37}FN_2O_7S_2Na$ [M + Na^+] 631.1918, found 631.1940 (3.35 ppm).

(+)-1-((2R,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ***(18)****.* A solution of **17** (20 mg, 0.03 mmol, 1.0 equiv) in 2,6-lutidine (1.0 mL, 0.03 M) was refluxed for 4 h at 160 °C. Upon cooling to room temperature, the reaction mixture was concentrated. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **18** (10.5 mg, 70%): R_f = 0.33 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +60 (*c* 1.1, $CDCl_3$); $C_{24}H_{25}FN_2O_4S$; MW = 456.5324 g/mol; IR (neat) ν_{max} 3183, 3065, 2861, 1691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.85 (s, 1H), 7.39−7.27 (m, 10H), 6.46 (dd, *J* = 14.4, 5.0 Hz, 1H), 5.09 (dt, *J* = 50.8, 5.1 Hz, 1H), 4.68 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.56−4.49 (m, 2H), 4.33−4.27 (m, 1H), 3.71−3.62 (m, 2H), 3.57 (appq, *J* = 5.1 Hz, 1H), 1.75 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 150.9, 138.0 (d, *J* = 2.1 Hz), 137.6, 137.1, 128.75, 128.74, 128.4, 128.29, 128.25, 128.0, 110.7, 95.9 (d, *J* = 193.8 Hz), 80.8 (d, *J* = 22.7 Hz), 73.6, 72.8, 69.6, 59.7 (d, *J* = 16.9 Hz), 48.4, 12.4 ppm; HRMS calcd for $C_{24}H_{25}FN_2O_4S$ Na [M + Na^+] 479.1411, found 479.1423 (2.36 ppm).

(+)-1-((2R,3S,4S,5R)-3-Fluoro-4-hydroxy-5-(hydroxymethyl)-tetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ***(19)****.* To a solution of **18** (26.3 mg, 0.058 mmol, 1.0 equiv) in anhydrous DCM (0.60 mL, 0.10 M) at −78 °C was added BBr_3 (0.25 mL, 0.23 mmol, 4.0 equiv, 1.0 M solution in DCM). The reaction was stirred for 2 h at −78 °C. A 1:1 mixture of MeOH/DCM (1.0 mL) and Ag_2CO_3 (0.24 g, 0.86 mmol, 15.0 equiv) was added, and the reaction mixture was increased to room temperature with stirring for 30 min followed by filtration on Celite and concentration. Purification by flash chromatography (DCM/MeOH, 90:10) provided **19** (9.1 mg, 57%). ^1H and ^{13}C NMR spectroscopic data correlate with the previously reported data.[5]

19: R_f = 0.41 (DCM/MeOH, 90:10); $[\alpha]_D^{25}$ +37 (*c* 0.8, CD_3OD); $C_{10}H_{13}FN_2O_4S$; MW = 276.2824 g/mol; IR (neat) ν_{max} 3360, 3054, 1681 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 8.26 (s, 1H), 6.34 (dd, *J* = 7.5, 6.0 Hz, 1H), 5.17 (ddd, *J* = 50.4, 7.2, 6.0 Hz, 1H), 4.41 (appdt, *J* = 12.5, 7.1 Hz, 1H), 3.94 (appd, *J* = 4.5 Hz, 2H), 3.41 (dt, *J* = 6.4, 4.8 Hz, 1H), 1.92 (s, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 166.1, 152.9, 140.0 (d, *J* = 1.4 Hz), 111.0, 97.5 (d, *J* = 194.9 Hz), 74.5 (d, *J* = 23.0 Hz), 62.1, 59.7 (d, *J* = 16.9 Hz), 52.6 (d, *J* = 4.1 Hz), 12.4 ppm; HRMS calcd for $C_{10}H_{14}FN_2O_4S$ [M + H^+] 277.0653, found 277.0650 (−0.95 ppm).

Synthesis of D-1′,2′-trans-Furanoside ***22*** *(Scheme 6). (−)-1-((1S,2R,3R,4R)-3,5-Bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione* ***(20)****.* To a solution of **15a** (76 mg, 0.12 mmol, 1.0 equiv) in anhydrous THF (1.2 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.24 mL, 2 mL/mmol, ∼70% HF). The reaction was stirred for 16 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided **20** (51.5 mg, 83%): R_f = 0.22 (hexanes/EtOAc, 60:40); $[\alpha]_D^{25}$ −17 (*c* 1.2, $CDCl_3$); $C_{28}H_{35}FN_2O_5S$; MW = 530.6513 g/mol; IR (neat) ν_{max} 3435, 3194, 2931, 1680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.56 (s, 1H), 7.36−7.21 (m, 10H), 6.35 (appd, *J* = 30.8 Hz, 1H), 4.86−4.71 (m, 2H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.54−4.47 (m, 2H), 4.18 (apps, 1H), 3.99 (apps, 1H), 3.59 (dd, *J* = 11.5, 6.4 Hz, 2H), 2.61 (d, *J* = 3.5 Hz, 1H), 1.92 (s, 3H), 1.22 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6, 150.3, 138.3, 137.9, 137.7, 128.612, 128.610, 127.99, 127.98, 127.91, 127.5, 111.2, 95.3 (d, *J* = 182.6 Hz), 78.4 (d, *J* = 23.5 Hz), 73.7, 73.6, 70.6 (d, *J* = 4.7 Hz), 70.3, 58.9 (d, *J* = 15.9 Hz), 45.0, 31.1, 12.8 ppm; HRMS calcd for $C_{28}H_{35}FN_2O_5SNa$ [M + Na^+] 553.2143, found 553.2153 (1.8 ppm).

(+)-1-((2R,3R,4R,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione ***(21)****.* To a solution of **20** (47 mg, 0.09 mmol, 1.0 equiv) in anhydrous THF (1.0 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (35 mg, 0.18 mmol, 2.0 equiv). The reaction was stirred for 5 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided **21** (28 mg, 71%): R_f = 0.28 (hexanes/EtOAc, 60:40); $[\alpha]_D^{25}$ +60 (*c* 1.2, $CDCl_3$); $C_{24}H_{25}FN_2O_5$; MW = 440.4641 g/mol; IR (neat) ν_{max} 3183, 3033, 2920, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.55 (d, *J* = 1.1 Hz, 1H), 7.39−7.23 (m, 10H), 6.07 (dd, *J*

DOI: 10.1021/acs.joc.6b01845
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= 16.3, 1.9 Hz, 1H), 5.05 (ddd, J = 52.3, 4.0, 1.9 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.55 (dt, J = 17.6, 8.1 Hz, 3H), 4.30 (d, J = 6.7 Hz, 1H), 4.22 (ddd, J = 18.6, 7.5, 4.1 Hz, 1H), 3.94 (dd, J = 11.1, 1.9 Hz, 1H), 3.67 (dd, J = 11.1, 2.3 Hz, 1H), 1.52 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 150.0, 137.4, 137.2, 135.8, 128.80, 128.75, 128.4, 128.3, 128.0, 127.9, 111.1, 91.8 (d, J = 192.3 Hz), 88.7 (d, J = 34.1 Hz), 81.2 (d, J = 1.4 Hz), 74.9 (d, J = 15.8 Hz), 73.9, 73.1 (d, J = 1.1 Hz), 68.2, 12.1 ppm; HRMS calcd for $C_{24}H_{25}FN_2O_5Na$ [M + Na$^+$] 463.1640, found 463.1631 (−1.9 ppm).

*(+)-1-((2R,3R,4R,5R)-3-Fluoro-4-hydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**22**).* To a solution of **21** (29 mg, 0.07 mmol, 1.0 equiv) in anhydrous DCM (0.70 mL, 0.10 M) at −78 °C was added BBr_3 (0.26 mL, 0.26 mmol, 4.0 equiv, 1 M soln in DCM). The reaction was stirred for 4 h at −78 °C and a 1:1 mixture of MeOH/DCM (1.0 mL) was added followed by $AgCO_3$ (0.28 g, 0.97 mmol, 15.0 equiv). Stirring was continued for 30 min at 25 °C followed by filtration on Celite and concentration. Purification by flash chromatography (DCM/MeOH, 90:10) provided **22** (10 mg, 60%): R_f = 0.26 (DCM/MeOH, 90:10); $[\alpha]_D^{25}$ +20 (c 1.0, CD_3OD); $C_{10}H_{13}FN_2O_5$; MW = 260.2214 g/mol; IR (neat) ν_{max} 3392, 3070, 2936, 1696, 1664 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.89 (s, 1H), 6.01 (dd, J = 17.6, 2.0 Hz, 1H), 5.03 (ddd, J = 53.2, 4.5, 2.0 Hz, 1H), 4.35 (ddd, J = 19.7, 7.6, 4.6 Hz, 1H), 4.02 (d, J = 7.6 Hz, 1H), 3.97 (dd, J = 12.5, 2.2 Hz, 1H), 3.79 (dd, J = 12.5, 3.0 Hz, 1H), 1.89 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in CD_3OD*. The proton NMR data in $(CD_3)_2SO$ have previously been reported;[44] however, we observed slight differences in the coupling constants: ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 11.35 (s, 1H), 7.78 (s, 1H), 5.91 (dd, J = 17.6, 2.2 Hz, 1H), 5.59 (d, J = 6.3 Hz, 1H), 5.23 (t, J = 5.1 Hz, 1H), 5.01 (ddd, J = 53.2, 4.3, 2.2 Hz, 1H), 4.22−4.12 (m, 1H), 3.86 (d, J = 7.2 Hz, 1H), 3.76 (dd, J = 7.2, 5.0 Hz, 1H), 3.62−3.55 (m, 1H), 1.75 (s, 3H) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ 166.4, 152.2, 138.3, 111.4, 95.0 (d, J = 186.8 Hz), 89.6 (d, J = 34.4 Hz), 84.7, 69.5 (d, J = 16.7 Hz), 61.1, 12.4 ppm; HRMS calcd for $C_{10}H_{13}FN_2O_5Na$ [M + Na$^+$] 283.0701, found 283.0698 (−0.87 ppm).

*Cyclization of 1,2-anti-Thioaminals **13b** and **15b** (Scheme 7). (−)-1-((1S,2S,3R,4S)-3,5-Bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**23**).* To a solution of **13b** (64 mg, 0.099 mmol, 1.0 equiv) in anhydrous THF (1.0 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.20 mL, 2 mL/mmol, ∼70% HF). The reaction was stirred for 16 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **23** (36.1 mg, 69%): R_f = 0.14 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −35 (c 0.9, $CDCl_3$); $C_{28}H_{35}FN_2O_5S$; MW = 530.6554 g/mol; IR (neat) ν_{max} 3425, 3188, 2925, 1684 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.44 (s, 1H), 7.38−7.27 (m, 10H), 6.23 (dd, J = 22.7, 4.8 Hz, 1H), 4.93 (appdt, J = 46.2, 5.1 Hz, 1H), 4.68 (d, J = 11.1 Hz, 1H), 4.61 (d, J = 11.2 Hz, 1H), 4.50 (apps, 2H), 4.23−4.17 (m, 1H), 3.80−3.73 (m, 1H), 3.54 (appd, J = 5.7 Hz, 2H), 2.46 (d, J = 6.3 Hz, 1H), 1.95 (s, 3H), 1.31 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 150.7, 137.95, 137.92, 137.5, 128.63, 128.58, 128.13, 128.05, 128.02, 127.96, 111.6, 94.8 (d, J = 185.3 Hz), 77.4, 74.5, 73.4, 70.8 (d, J = 3.2 Hz), 69.1 (d, J = 4.1 Hz), 57.2 (d, J = 19.5 Hz), 45.7, 31.2, 12.8 ppm; HRMS calcd for $C_{28}H_{35}FN_2O_5SNa$ [M + Na$^+$] 553.2143, found 553.2157 (2.49 ppm).

*(−)-(2S,3R,4S,5S)-1,3-Bis(benzyloxy)-5-(tert-butylthio)-4-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)pentan-2-yl Methanesulfonate (**24**).* To a solution of **23** (38 mg, 0.072 mmol, 1.0 equiv) in anhydrous DCM (0.30 mL, 0.30 M) at 0 °C were added triethylamine (20 μL, 0.14 mmol, 2.0 equiv) and methanesulfonyl chloride (10 μL, 0.11 mmol, 1.5 equiv). The reaction was stirred for 5 h at 25 °C. A 1.0 N solution (0.25 mL) of HCl was added, and the aqueous layer was extracted with dichloromethane (3 × 0.50 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **24** (24.9 mg, 57%): R_f = 0.41 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −32 (c 0.95, $CDCl_3$); $C_{29}H_{37}FN_2O_7S_2$; MW = 608.7404 g/mol; IR (neat) ν_{max} 3178, 3027, 2925, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.44 (s, 1H), 7.37−7.24 (m, 10H), 6.37 (dd, J = 17.0, 6.7 Hz, 1H), 5.07−5.02 (m, 1H), 4.76 (ddd, J = 46.3, 6.8, 3.1 Hz, 1H), 4.75 (d, J = 11.4 Hz, 1H), 4.68 (d, J = 11.5 Hz, 1H), 4.49 (d, J = 11.8 Hz, 1H), 4.43 (d, J = 11.8 Hz, 1H), 4.12−4.02 (m, 1H), 3.77−3.69 (m, 2H), 3.00 (s, 3H), 1.96 (s, 3H), 1.30 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 150.9, 137.4, 137.2, 137.0, 128.73, 128.70, 128.4, 128.2, 128.0, 127.9, 111.7, 92.1 (d, J = 188.0 Hz), 79.6, 76.4 (d, J = 16.8 Hz), 74.5, 73.4, 68.7 (d, J = 6.1 Hz), 57.1 (d, J = 20.8 Hz), 46.2, 38.4, 31.2, 12.8 ppm; HRMS calcd for $C_{29}H_{37}FN_2O_7S_2Na$ [M + Na$^+$] 631.1918, found 631.1936 (2.77 ppm).

*1-((2S,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**25**).* A solution of **24** (20 mg, 0.032 mmol, 1.0 equiv) in 2,6-lutidine (1.0 mL, 0.03 M) was refluxed for 48 h at 160 °C. Upon cooling to room temperature, the reaction mixture was concentrated and a 2:1 mixture of product **25** and starting material **24** was obtained. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided an inseparable mixture (11.5 mg): R_f = 0.30 (hexanes/EtOAc, 50:50); $C_{24}H_{25}FN_2O_4S$; MW = 456.5324 g/mol; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H, product), 8.08 (s, 1H, starting material), 7.58 (s, 1H, product), 7.44 (s, 1H, starting material), 7.39−7.22 (m, 20H, product and starting material), 6.40−6.35 (m, 1H, starting material), 6.33 (dd, J = 17.0, 2.8 Hz, 1H, product), 5.09 (dt, J = 48.0, 3.0 Hz, 2H, product and starting material), 4.76 (ddd, J = 46.3, 6.9, 3.3 Hz, 1H, starting material), 4.75 (d, J = 11.5 Hz, 1H, starting material), 4.68 (d, J = 11.5 Hz, 1H, starting material), 4.60 (q, J = 11.2 Hz, 2H, product), 4.54 (apps, 2H, product), 4.46 (dd, J = 31.1, 11.8 Hz, 2H, starting material), 4.32 (appdt, J = 11.6, 3.3 Hz, 1H, product), 4.07 (appdt, J = 8.0, 3.0 Hz, 1H, starting material), 3.98−3.93 (m, 1H, product), 3.77−3.71 (m, 2H, starting material), 3.66 (t, J = 8.8 Hz, 1H, product), 3.55−3.50 (m, 1H, product), 3.00 (s, 3H, starting material), 1.96 (s, 3H, starting material), 1.74 (s, 3H, product), 1.31 (d, J = 7.3 Hz, 9H, starting material) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.16 (product), 163.15 (starting material), 150.9 (starting material), 150.6 (product), 137.7 (product), 137.5 (product), 137.4 (starting material), 137.2(starting material), 137.0 (starting material), 136.6 (product), 128.8 (product), 128.73 (starting material), 128.69 (starting material), 128.65 (product), 128.5 (product), 128.3 (starting material), 128.19 (product), 128.18 (starting material), 128.1 (product), 128.0 (starting material), 127.88 (product), 127.87 (starting material), 111.7 (starting material), 111.0 (product), 100.7 (d, J = 190.5 Hz, product), 92.1 (d, J = 187.6 Hz, starting material),83.3 (d, J = 26.5 Hz, product), 79.6 (starting material), 76.4 (d, J = 17.4 Hz, starting material), 74.5 (starting material), 73.6 (d, J = 3.1 Hz, product), 73.4 (starting material), 72.9 (product), 71.4 (product), 68.7 (d, J = 6.0 Hz, starting material), 64.9 (d, J = 32.2 Hz, product), 57.1 (d, J = 20.1 Hz, starting material), 52.0 (product), 46.2 (starting material), 38.4 (starting material), 31.2 (starting material), 12.8 (starting material), 12.5 (product) ppm; HRMS calcd for $C_{24}H_{25}FN_2O_4SNa$ [M + Na$^+$] 479.1411, found 479.1416 (1.01 ppm).

*(+)-1-((1R,2R,3R,4R)-3,5-Bis(benzyloxy)-1-(tert-butylthio)-2-fluoro-4-hydroxypentyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**26**).* To a solution of **15b** (31 mg, 0.05 mmol, 1.0 equiv) in anhydrous THF (0.50 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.10 mL, 2 mL/mmol, ∼70% HF). The reaction was stirred for 16 h at 25 °C. A saturated solution (0.50 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 0.50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided **26** (18.1 mg, 71%): R_f = 0.22 (hexanes/EtOAc, 60:40); $[\alpha]_D^{25}$ +81 (c 1.2, $CDCl_3$); $C_{28}H_{35}FN_2O_5S$; MW = 530.6513 g/mol; IR (neat) ν_{max} 3419, 3182, 2961, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.47 (s, 1H), 7.37−7.14 (m, 10H), 6.37 (dd, J = 25.2, 3.5 Hz, 1H), 5.02 (dt, J = 44.7, 3.6 Hz, 1H), 4.58 (d, J = 10.9 Hz, 1H), 4.55 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 10.9 Hz, 1H), 4.24−4.17 (m, 1H), 3.91 (ddd, J = 14.3, 7.7, 3.0 Hz, 1H), 3.65−3.55 (m, 2H), 2.77 (d, J = 5.5

DOI: 10.1021/acs.joc.6b01845
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Hz, 1H), 1.86 (s, 3H), 1.31 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 150.8, 138.6, 137.8, 137.4, 128.6, 128.5, 128.2, 128.12, 128.09, 128.06, 110.8, 95.9 (d, J = 181.8 Hz), 79.1 (d, J = 19.7 Hz), 74.6, 73.6, 70.7, 69.8 (d, J = 8.9 Hz), 56.4 (d, J = 19.2 Hz), 45.8, 31.1, 12.7 ppm; HRMS calcd for $C_{28}H_{35}FN_2O_5SNa$ [M + Na$^+$] 553.2143, found 553.2151 (1.4 ppm).

*(+)-1-((2S,3R,4R,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**27**).* To a solution of **26** (17 mg, 0.03 mmol, 1.0 equiv) in anhydrous THF (0.32 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (13 mg, 0.06 mmol, 2.0 equiv). The reaction was stirred for 5 h at 25 °C. A saturated solution (0.50 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 0.50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided **27** (8.9 mg, 64%): R_f = 0.28 (hexanes/EtOAc, 60:40); $[\alpha]_D^{25}$ +29 (c 0.7, $CDCl_3$); $C_{24}H_{25}FN_2O_5$; MW = 440.4641 g/mol; IR (neat) ν_{max} 3193, 3038, 2861, 1685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.41−7.27 (m, 11H), 6.25 (dd, J = 17.8, 3.5 Hz, 1H), 5.15 (dt, J = 53.9, 3.6 Hz, 1H), 4.69 (d, J = 11.5 Hz, 1H), 4.57 (appt, J = 11.3 Hz, 2H), 4.51 (d, J = 12.0 Hz, 1H), 4.46−4.42 (m, 1H), 4.25 (ddd, J = 19.3, 6.9, 3.8 Hz, 1H), 3.73 (dd, J = 10.9, 2.2 Hz, 1H), 3.57 (dd, J = 11.0, 3.3 Hz, 1H), 1.88 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.5, 150.3, 137.6, 136.9, 136.8, 128.8, 128.7, 128.6, 128.2, 128.1, 127.9, 110.2, 88.7 (d, J = 196.9 Hz), 84.6 (d, J = 15.6 Hz), 81.6, 77.0, 73.9, 73.3 (d, J = 1.2 Hz), 69.1, 12.6 ppm; HRMS calcd for $C_{24}H_{25}FN_2O_5Na$ [M + Na$^+$] 463.1640, found 463.1645 (1.1 ppm).

*Synthesis of Novel D-1′,2′-cis-Thiofuranosides through a S1′−C4 Cyclization (Scheme 8). (+)-(R)-4-Hydroxydihydrofuran-2(3H)-one (**28**).* Following a slightly modified literature procedure,[45] a solution of L-carnitine (9.5 g, 59.1 mmol, 1.0 equiv) in DMF (95 mL, 0.62 M) was heated to 150 °C for 16 h and concentrated. Purification by flash chromatography (hexanes/EtOAc, 0:100) provided the known compound **28** (4.2 g, 70%). Characterization data correlate with the previously reported data:[45] R_f = 0.28 (hexanes/EtOAc, 0:100); $[\alpha]_D^{25}$ +79 (c = 0.9, MeOH); $C_4H_6O_3$; MW = 102.0886 g/mol; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.70−4.66 (m, 1H), 4.42 (dd, J = 10.3, 4.5 Hz, 1H), 4.30 (appd, J = 10.3 Hz, 1H), 2.86 (d, J = 3.8 Hz, 1H), 2.75 (dd, J = 17.9, 6.1 Hz, 1H), 2.52 (dd, J = 18.0, 1.0 Hz, 1H) ppm.

*(+)-(3R,4R)-3-Allyl-4-hydroxydihydrofuran-2(3H)-one (**S6**).* To LiHMDS (70 mL, 69 mmol, 2.4 equiv, 1 M THF) at −78 °C was added a solution of **28** (2.95 g, 29 mmol, 1.0 equiv) in anhydrous THF (47 mL, 0.61 M). Stirring was maintained for 1 h at −40 °C. AllylBr (3.3 mL, 38 mmol, 1.3 equiv) and DMI (7.0 mL, 64 mmol, 2.2 equiv) were added as a solution in anhydrous THF (16 mL, 2.4 M) and stirred for 2 h at −40 °C. The reaction mixture was quenched with 1 N HCl (20 mL) and concentrated. The aqueous layer was extracted with isopropyl acetate (4 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 20:80) provided **S6** (3.3 g, 80%): R_f = 0.52 (hexanes/EtOAc, 20:80); $[\alpha]_D^{25}$ +29 (c = 1.4, $CDCl_3$); $C_7H_{10}O_3$; MW = 142.1525 g/mol; IR (neat) ν_{max} 3442, 2911, 1759 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90−5.78 (m, 1H), 5.20 (appd, J = 17.0 Hz, 1H), 5.16 (appd, J = 10.3 Hz, 1H), 4.46−4.37 (m, 2H), 4.08 (dd, J = 8.5, 3.8 Hz, 1H), 2.67−2.56 (m, 2H), 2.40−2.25 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 134.0, 118.7, 72.8, 71.9, 48.1, 32.6 ppm; HRMS calcd for $C_7H_{10}O_3Na$ [M + Na$^+$] 165.0522, found 165.0523 (0.47 ppm).

*(+)-(3S,4R)-3-Allyl-4-hydroxy-3-methyldihydrofuran-2(3H)-one (**29**).* To a solution of DIPA (13.5 mL, 94.9 mmol, 2.5 equiv) in anhydrous THF (95 mL, 1.0 M) at −78 °C was added n-BuLi (38 mL, 94.9 mmol, 2.5 equiv, 2.5 M solution in hexanes). The reaction mixture was stirred at −40 °C for 1 h. **S6** (5.4 g, 38 mmol, 1.0 equiv) as a solution in anhydrous THF (76 mL, 0.5 M) was added and stirred for 2 h at −40 °C. A solution of MeI (3.8 mL, 61 mmol, 1.6 equiv) and DMI (9.2 mL, 84 mmol, 2.2 equiv) in anhydrous THF (76 mL, 0.80 M) was added and stirred for 3 h at −35 °C. The reaction mixture was quenched with 6 N HCl (20 mL) and concentrated. The aqueous layer was extracted with isopropyl acetate (4 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/Et_2O, 30:70) provided **29** (3.97 g, 67%): R_f = 0.26 (hexanes/Et_2O, 30:70); $[\alpha]_D^{25}$ +47 (c = 1.3, $CDCl_3$); $C_8H_{12}O_3$; MW = 156.1810 g/mol; IR (neat) ν_{max} 3447, 2978, 2928, 1752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98−5.85 (m, 1H), 5.27−5.17 (m, 2H), 4.43 (dd, J = 10.2, 4.5 Hz, 1H), 4.22 (apps, 1H), 4.18 (dd, J = 10.2, 2.0 Hz, 1H), 2.54 (dd, J = 14.3, 7.6 Hz, 1H), 2.42 (dd, J = 14.3, 7.0 Hz, 1H), 2.23 (d, J = 3.6 Hz, 1H), 1.23 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.0, 133.4, 119.4, 75.6, 72.4, 46.7, 35.9, 20.2 ppm; HRMS calcd for $C_8H_{12}O_3Na$ [M + Na$^+$] 179.0679, found 179.0680 (0.97 ppm).

*(−)-(2R,3R)-3-Allyl-3-methylbutane-1,2,4-triol (**S7**).* To a solution of **29** (6.1 g, 39 mmol, 1.0 equiv) in anhydrous THF (130 mL, 0.30 M) at 0 °C was added $LiAlH_4$ (30 mL, 58.7 mmol, 1.5 equiv, 1 M solution in THF). The reaction was stirred for 4 h at 10 °C, quenched with $Na_2SO_4{\cdot}10H_2O$ (30 g), and stirred for an additional 1.5 h at 25 °C. After dilution with EtOAc, the mixture was dried over Na_2SO_4, washed with THF (3 × 50 mL), filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **S7** (4.4 g, 70%): R_f = 0.33 (hexanes/EtOAc, 0:100); $[\alpha]_D^{25}$ −11 (c 1.2, $CDCl_3$); $C_8H_{16}O_3$; MW = 160.2108 g/mol; IR (neat) ν_{max} 3328, 2931, 2888, 1638 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92−5.80 (m, 1H), 5.13 (dd, J = 3.7, 2.9 Hz, 1H), 5.10 (apps, 1H), 3.78−3.66 (m, 2H), 3.60 (dd, J = 6.8, 3.4 Hz, 1H), 3.56 (d, J = 11.1 Hz, 1H), 3.53 (d, J = 11.4 Hz, 1H), 2.24 (dd, J = 13.8, 7.4 Hz, 1H), 2.14 (dd, J = 13.7, 7.5 Hz, 1H), 0.85 (s, 3H) ppm *OH signals missing possibly due to exchange in CDCl$_3$*; ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.0, 118.5, 77.1, 68.2, 62.7, 40.8, 40.3, 17.9 ppm; HRMS calcd for $C_8H_{16}O_3Na$ [M + Na$^+$] 183.0992, found 183.0992 (0.23 ppm).

*(−)-(2R,3R)-2-Allyl-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**S8**).* To a solution of **S7** (1.9 g, 12.1 mmol, 1.0 equiv) in anhydrous DCM (15 mL, 0.80 M) at −40 °C was added NEt_3 (13.5 mL, 96.6 mmol, 8.0 equiv) followed by stirring for 30 min. BzCl (3.1 mL, 26.6 mmol, 2.2 equiv) was added, and the reaction mixture was placed at −20 °C for 16 h. The reaction was quenched with 1 N HCl solution (10 mL), and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **S8** (3.6 g, 80%): R_f = 0.48 (hexanes/EtOAc,, 70:30); $[\alpha]_D^{25}$ −8 (c 1.2, $CDCl_3$); $C_{22}H_{24}O_5$; MW = 368.4290 g/mol; IR (neat) ν_{max} 3505, 3065, 2973, 1718 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07−8.03 (m, 4H), 7.60−7.55 (m, 2H), 7.45 (dt, J = 14.1, 7.7 Hz, 4H), 5.96−5.86 (m, 1H), 5.18 (appd, J = 3.7 Hz, 1H), 5.15 (apps, 1H), 4.66 (dd, J = 11.5, 2.3 Hz, 1H), 4.47 (d, J = 11.3 Hz, 1H), 4.40 (dd, J = 11.5, 8.7 Hz, 1H), 4.19 (d, J = 11.3 Hz, 1H), 3.95 (appd, J = 8.6 Hz, 1H), 2.70 (d, J = 3.5 Hz, 1H), 2.35 (dd, J = 13.7, 7.5 Hz, 1H), 2.29 (dd, J = 13.7, 7.6 Hz, 1H), 1.09 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.8, 133.5, 133.4, 133.3, 130.1, 130.0, 129.82, 129.77, 128.7, 128.6, 119.2, 73.3, 67.8, 66.7, 41.1, 39.5, 17.3 ppm; HRMS calcd for $C_{22}H_{24}O_5Na$ [M + Na$^+$] 391.1516, found 391.1516 (0.02 ppm).

*(−)-(2R,3R)-2-Allyl-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl Dibenzoate (**30**).* To a solution of **S8** (0.60 g, 1.63 mmol, 1.0 equiv) in anhydrous DCM (8.2 mL, 0.20 M) at 0 °C were added imidazole (0.28 g, 4.1 mmol, 2.5 equiv) and TESCl (0.40 mL, 2.1 mmol, 1.3 equiv) The reaction mixture was stirred at 25 °C for 16 h. A saturated solution of NH_4Cl (5 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **30** (0.69 g, 88%): R_f = 0.43 (hexanes/EtOAc, 90:10); $[\alpha]_D^{25}$ −17 (c 1.3, $CDCl_3$); $C_{28}H_{38}O_5Si$; MW = 482.6920 g/mol; IR (neat) ν_{max} 2958, 2877, 1717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08−8.02 (m, 4H), 7.60−7.54 (m, 2H), 7.45 (td, J = 7.8, 3.4 Hz, 4H), 5.92−5.81 (m, 1H), 5.12−5.05 (m, 2H), 4.66 (dd, J = 11.7, 2.9 Hz, 1H), 4.32 (dd, J = 11.7, 6.7 Hz, 1H), 4.26 (d, J = 11.1 Hz, 1H), 4.22 (d, J = 11.1 Hz, 1H), 4.11 (dd, J = 6.6, 2.8 Hz, 1H), 2.36−2.26 (m, 2H), 1.08 (s, 3H), 0.91 (t, J = 8.0 Hz, 9H), 0.67−0.57 (m, 6H) ppm;

DOI: 10.1021/acs.joc.6b01845
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^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.5, 133.6, 133.2, 133.1, 130.4, 130.2, 129.8, 129.7, 128.57, 128.55, 118.8, 74.4, 68.0, 67.7, 41.7, 39.2, 17.7, 7.1, 5.4 ppm; HRMS calcd for $C_{28}H_{38}O_5SiNa$ [M + Na^+] 505.2381, found 505.2378 (−0.55 ppm).

*(−)-(2R,3R)-2-Methyl-2-(2-oxoethyl)-3-((triethylsilyl)oxy)butane-1,4-diyl Dibenzoate (**31**).* To a solution of **30** (0.69 g, 1.4 mmol, 1.0 equiv) in DCM (50 mL, 0.03 M) at −78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 25 min). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (1.2 mL, 8.6 mmol, 6.0 equiv), the reaction was warmed to 25 °C for 1 h and concentrated. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **31** (0.58 g, 83%): R_f = 0.33 (hexanes/EtOAc, 80:20); $[\alpha]_D^{25}$ −17 (*c* 0.9, $CDCl_3$); $C_{27}H_{36}O_6Si$; MW = 484.6566 g/mol; IR (neat) ν_{max} 2952, 2872, 1719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (t, *J* = 2.5 Hz, 1H), 8.05−7.97 (m, 4H), 7.59−7.54 (m, 2H), 7.46−7.42 (m, 4H), 4.61 (dd, *J* = 11.9, 4.0 Hz, 1H), 4.45−4.33 (m, 3H), 4.18 (dd, *J* = 5.4, 4.1 Hz, 1H), 2.70 (dd, *J* = 15.5, 2.8 Hz, 1H), 2.53 (dd, *J* = 15.5, 2.4 Hz, 1H), 1.32 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.69−0.60 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 166.6, 166.3, 133.35, 133.31, 129.9, 129.9, 129.8, 129.7, 128.7, 128.6, 74.6, 68.6, 66.8, 48.4, 42.5, 19.8, 7.0, 5.2 ppm; HRMS calcd for $C_{27}H_{36}O_6SiNa$ [M + Na^+] 507.2173, found 507.2182 (1.80 ppm).

*(−)-(2R,3R)-2-((S)-1-Fluoro-2-oxoethyl)-2-methyl-3-((triethylsilyl)-oxy)butane-1,4-diyl Dibenzoate (**S9**).* To the (*S*)-imidazolidinone catalyst (68 mg, 0.31 mmol, 1.3 equiv) at −40 °C was added **31** (0.12 g, 0.24 mmol, 1.0 equiv) as a solution in anhydrous DMF (0.25 mL, 1.0 M). After being stirred for 10 min, NFSI (84 mg, 0.25 mmol, 1.05 equiv) was added. Once homogeneous, it was left at −20 °C for 72 h. The reaction mixture was diluted with Et_2O and water (1.0 mL) and treated with Me_2S (40 μL, 0.48 mmol, 2.0 equiv). The aqueous layer was extracted with Et_2O (3 × 1 mL), and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified C2−F aldehyde indicated ∼17:1 diastereomeric ratio for the fluorination. Some of the C2−F aldehyde was isolated and characterized: **S9**: R_f = 0.44 (hexanes/EtOAc, 80:20); $[\alpha]_D^{25}$ −31.3 (*c* 1.42, $CDCl_3$); $C_{27}H_{35}FO_6Si$; MW = 502.6544 g/mol; IR (neat) ν_{max} 2958, 2877, 1723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (dd, *J* = 7.5, 0.9 Hz, 1H), 8.00 (ddd, *J* = 19.8, 9.9, 5.7 Hz, 4H), 7.61−7.55 (m, 2H), 7.46 (dd, *J* = 16.2, 8.2 Hz, 4H), 4.97 (d, *J* = 48.0 Hz, 1H), 4.63 (dd, *J* = 12.1, 3.9 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.48 (dd, *J* = 11.5, 2.2 Hz, 1H), 4.40 (dd, *J* = 12.7, 4.9 Hz, 1H), 4.26−4.22 (m, 1H), 1.30 (s, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.68 (q, *J* = 7.9 Hz, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2 (d, *J* = 35.8 Hz), 166.6, 166.2, 133.6, 133.5, 129.9, 129.85, 129.83, 129.78, 128.82, 128.79, 95.5 (d, *J* = 181.3 Hz), 73.0, 66.7 (d, *J* = 3.1 Hz), 65.1 (d, *J* = 5.0 Hz), 48.1 (d, *J* = 17.9 Hz), 16.0 (d, *J* = 5.5 Hz), 7.0, 5.2 ppm; HRMS calcd for $C_{27}H_{35}FO_6SiNa$ [M + Na^+] 525.2079, found 525.2079 (−0.09 ppm).

*(+)-(2R,3R)-2-((R)-1-Fluoro-2-oxoethyl)-2-methyl-3-((triethylsilyl)-oxy)butane-1,4-diyl Dibenzoate (**S10**).* To the (*R*)-imidazolidinone catalyst (0.14 g, 0.64 mmol, 1.2 equiv) at −40 °C, was added **31** (0.25 g, 0.52 mmol, 1.0 equiv) as a solution in anhydrous DMF (0.6 mL, 1.0 M). After being stirred for 10 min, NFSI (0.17 g, 0.55 mmol, 1.05 equiv) was added. Once homogeneous, it was left at −20 °C for 72 h. The reaction mixture was diluted with Et_2O and water (1.0 mL) and treated with Me_2S (80 μL, 1.04 mmol, 2.0 equiv). The aqueous layer was extracted with Et_2O (3 × 1 mL), and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopic analysis of the unpurified C2−F aldehyde indicated ∼17:1 diastereomeric ratio for the fluorination. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **S10** (0.16 g, 62%): R_f = 0.23 (hexanes/EtOAc,90:10); $[\alpha]_D^{25}$ +2.4 (*c* 1.1, $CDCl_3$); $C_{27}H_{35}FO_6Si$; MW = 502.6471 g/mol; IR (neat) ν_{max} 2958, 2877, 1721 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (d, *J* = 6.5 Hz, 1H), 8.01 (dd, *J* = 23.4, 8.0 Hz, 4H), 7.60−7.54 (m, 2H), 7.49−7.41 (m, 4H), 4.81 (d, *J* = 48.3 Hz, 1H), 4.68 (dd, *J* = 12.0, 3.9 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.50−4.45 (m, 2H), 4.22 (dd, *J* = 6.2, 4.1 Hz, 1H), 1.27 (d, *J* = 15.0 Hz, 3H), 0.96−0.88 (m, 9H), 0.71−0.56 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6 (d, *J* = 36.4 Hz), 166.5, 166.1, 133.44, 133.35, 129.9, 129.8, 129.73, 129.70, 128.7, 128.6, 95.9 (d, *J* = 184.4 Hz), 73.4, 67.2 (d, *J* = 6.2 Hz), 65.2 (d, *J* = 5.0 Hz), 48.5 (d, *J* = 17.9 Hz), 16.6 (d, *J* = 6.0 Hz), 6.9, 5.1 ppm; HRMS calcd for $C_{27}H_{35}FO_6SiNa$ [M + Na^+] 525.2079, found 525.2099 (3.74 ppm).

*(+)-(2R,3R)-2-((S)-2,2-Bis(tert-butylthio)-1-fluoroethyl)-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl Dibenzoate (**32**).* To the crude C2−F aldehyde **S9** in anhydrous DCM (2.4 mL, 0.10 M) at −70 °C were added *t*BuSH (100 μL, 0.97 mmol, 4.0 equiv) and $BF_3{\cdot}OEt_2$ (80 μL, 0.60 mmol, 2.5 equiv). The reaction was stirred at −60 °C for 3 h. Upon addition of NEt_3 (0.14 mL, 0.97 mmol, 4.0 equiv) stirring was maintained at −50 °C for 15 min. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **32** (108 mg, 68% for two steps): R_f = 0.52 (hexanes/EtOAc, 80:20); $[\alpha]_D^{25}$ +5 (*c* 1.3, $CDCl_3$); $C_{35}H_{53}FO_5S_2Si$; MW = 665.0074 g/mol; IR (neat) ν_{max} 2963, 2877, 1723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98−7.93 (m, 4H), 7.54−7.49 (m, 2H), 7.37 (dd, *J* = 16.1, 8.3 Hz, 4H), 5.37 (d, *J* = 43.9 Hz, 1H), 5.15 (d, *J* = 11.9 Hz, 1H), 4.71−4.65 (m, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.48−4.41 (m, 2H), 4.29 (dd, *J* = 29.3, 0.9 Hz, 1H), 1.45 (s, 9H), 1.42 (s, 9H), 1.28 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.70−0.60 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 166.4, 133.0, 132.95, 130.4, 130.2, 129.71, 129.65, 128.43, 128.40, 97.9 (d, *J* = 180.7 Hz), 74.1, 67.6 (d, *J* = 8.9 Hz), 66.2 (d, *J* = 7.3 Hz), 47.1 (d, *J* = 17.8 Hz), 46.9 (d, *J* = 2.5 Hz), 46.0, 44.8, 32.0, 31.7, 19.1 (d, *J* = 6.5 Hz), 7.0, 5.2 ppm; HRMS calcd for $C_{35}H_{53}FO_5S_2SiNa$ [M + Na^+] 687.2980, found 687.2990 (1.44 ppm).

*(+)-(2R,3R)-2-((1S,2R)-2-(tert-Butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methyl-3-((triethylsilyl)oxy)butane-1,4-diyl Dibenzoate (**33**).* Following general procedure A, silylated thymine (0.8 mL, 0.52 mmol, 3.0 equiv of a 0.67 M solution in THF) and I_2 (88 mg, 0.35 mmol, 2.0 equiv) were added to a solution of **32** (0.11 g, 0.17 mmol, 1.0 equiv) in anhydrous THF (1.8 mL, 0.10 M) and stirred at 25 °C for 16 h. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **33** (0.11 g, 92%): R_f = 0.23 (hexanes/EtOAc, 80:20); $[\alpha]_D^{25}$ +45 (*c* 1.0, $CDCl_3$); $C_{36}H_{49}FN_2O_7SSi$; MW = 700.9384 g/mol; IR (neat) ν_{max} 3188, 2958, 2877, 1717, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.96 (ddd, *J* = 24.7, 8.3, 1.0 Hz, 4H), 7.67 (s, 1H), 7.57−7.51 (m, 2H), 7.39 (dt, *J* = 22.5, 7.8 Hz, 4H), 6.15 (appd, *J* = 31.4 Hz, 1H), 5.02 (appd, *J* = 46.4 Hz, 1H), 4.81 (d, *J* = 11.7 Hz, 1H), 4.59−4.53 (m, 2H), 4.48 (dd, *J* = 5.9, 4.3 Hz, 1H), 4.40 (ddd, *J* = 11.7, 6.1, 2.6 Hz, 1H), 1.96 (s, 3H), 1.30 (s, 12H), 0.91 (t, *J* = 7.9 Hz, 9H), 0.68−0.59 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 166.3, 163.4, 150.1, 138.0 (d, *J* = 2.9 Hz), 133.2, 133.1, 130.2, 130.0, 129.7, 129.6, 128.52, 128.48, 111.3, 99.5 (d, *J* = 184.8 Hz), 72.7, 67.0 (d, *J* = 6.6 Hz), 65.6 (d, *J* = 4.8 Hz), 58.7 (d, *J* = 20.0 Hz), 45.8 (d, *J* = 16.8 Hz), 45.2, 31.0, 17.5 (d, *J* = 6.1 Hz), 12.8, 7.0, 5.3 ppm; HRMS calcd for $C_{36}H_{49}FN_2O_7SSiNa$ [M + Na^+] 723.2906, found 723.2927 (2.9 ppm).

*(+)-(2R,3R)-2-((1S,2R)-2-(tert-Butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**S11**).* To a solution of **33** (1.77 g, 2.53 mmol, 1.0 equiv) in anhydrous THF (25.0 mL, 0.10 M) in a plastic vial at 0 °C was added $3HF{\cdot}NEt_3$ (1.24 mL, 7.59 mmol, 3.0 equiv). The reaction was stirred for 16 h at 25 °C. A saturated solution (10 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **S11** (1.4 g, 91%): R_f = 0.27 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +15 (*c* 1.1, $CDCl_3$); $C_{30}H_{35}FN_2O_7S$; MW = 586.6754 g/mol; IR (neat) ν_{max} 3446, 3188, 2963, 1680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.12−7.98 (m, 4H), 7.69 (s, 1H), 7.59−7.53

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

(m, 2H), 7.43 (dt, J = 19.3, 7.8 Hz, 4H), 6.35 (appd, J = 29.8 Hz, 1H), 5.00 (appd, J = 47.3 Hz, 1H), 4.74 (dd, J = 11.6, 2.3 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 4.53 (d, J = 11.8 Hz, 1H), 4.49 (dd, J = 11.6, 8.3 Hz, 1H), 4.36−4.32 (m, 1H), 3.52 (d, J = 4.0 Hz, 1H), 1.96 (s, 3H), 1.35 (s, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.4, 163.5, 150.9, 137.7 (d, J = 2.1 Hz), 133.4, 133.3, 130.0, 129.89, 129.88, 129.83, 128.7, 128.5, 112.1, 99.1 (d, J = 185.0 Hz), 73.0 (d, J = 3.3 Hz), 66.9 (d, J = 4.0 Hz), 65.3 (d, J = 4.3 Hz), 58.5 (d, J = 19.8 Hz), 45.2292, 45.2291 (d, J = 17.3 Hz), 31.1, 16.1 (d, J = 4.7 Hz), 12.8 ppm; HRMS calcd for $C_{30}H_{35}FN_2O_7SNa$ [M + Na^+] 609.2041, found 609.2058 (2.84 ppm).

*(+)-(2R,3R)-2-((1S,2R)-2-(tert-Butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl Dibenzoate (**S12**).* To a solution of **S11** (36 mg, 0.06 mmol, 1.0 equiv) in anhydrous DCM (0.20 mL, 0.30 M) at 0 °C were added triethylamine (40 μL, 0.24 mmol, 4.0 equiv) and methanesulfonyl chloride (14 μL, 0.18 mmol, 3.0 equiv). The reaction was stirred for 16 h at 25 °C. A 1.0 N solution (0.20 mL) of HCl was added, and the aqueous layer was extracted with dichloromethane (3 × 1 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **S12** (20 mg, 50%): R_f = 0.17 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +34 (c 0.7, $CDCl_3$); $C_{31}H_{37}FN_2O_9S_2$; MW = 664.7619 g/mol; IR (neat) ν_{max} 3183, 2963, 1717, 1685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.05 (t, J = 7.6 Hz, 4H), 7.67 (s, 1H), 7.57 (t, J = 7.4 Hz, 2H), 7.47−7.41 (m, 4H), 6.25 (appd, J = 31.6 Hz, 1H), 5.56 (dd, J = 8.2, 1.7 Hz, 1H), 4.88 (appd, J = 46.7 Hz, 1H), 4.87 (dd, J = 12.8, 1.8 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 4.62−4.55 (m, 2H), 3.07 (s, 3H), 1.97 (s, 3H), 1.43 (s, 3H), 1.32 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 166.1, 163.2, 150.2, 137.5 (d, J = 2.3 Hz), 133.6, 133.5, 129.90, 129.88, 129.7, 129.4, 128.74, 128.69, 111.7, 99.7 (d, J = 186.3 Hz), 82.1, 65.5 (d, J = 4.7 Hz), 64.3 (d, J = 8.1 Hz), 58.3 (d, J = 20.2 Hz), 45.7, 45.2 (d, J = 17.4 Hz), 39.4, 31.1, 17.6 (d, J = 6.2 Hz), 12.8 ppm; HRMS calcd for $C_{31}H_{37}FN_2O_9S_2Na$ [M + Na^+] 687.1817, found 687.1842 (3.8 ppm).

*(+)-((2S,3S,4S,5R)-4-Fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrothiophene-2,3-diyl)bis(methylene) Dibenzoate (**34**).* A solution of **S12** (0.584 g, 0.88 mmol, 1.0 equiv) in 2,6-lutidine (9.0 mL, 0.10 M) was refluxed for 4 h at 160 °C. Upon cooling to 25 °C, the reaction mixture was concentrated. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **34** (0.39 g, 86%): R_f = 0.28 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +106 (c 1.2, $CDCl_3$); $C_{26}H_{25}FN_2O_6S$; MW = 512.5499 g/mol; IR (neat) ν_{max} 3215, 2979, 1717, 1685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.10−8.02 (m, 4H), 7.79 (s, 1H), 7.60 (t, J = 7.4 Hz, 2H), 7.47 (td, J = 7.8, 3.2 Hz, 4H), 6.65 (dd, J = 25.7, 4.0 Hz, 1H), 5.04 (dd, J = 51.5, 4.0 Hz, 1H), 4.80 (appt, J = 10.2 Hz, 1H), 4.63 (dd, J = 11.3, 5.7 Hz, 1H), 4.43 (apps, 2H), 3.72 (dd, J = 9.0, 5.7 Hz, 1H), 1.95 (s, 3H), 1.48 (d, J = 1.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 166.1, 163.3 (d, J = 1.1 Hz), 150.9, 138.7 (d, J = 4.5 Hz), 133.8, 133.6, 129.88, 129.86, 129.7, 129.3, 128.8, 128.7, 110.6, 98.5 (d, J = 190.9 Hz), 68.0 (d, J = 9.5 Hz), 65.9 (d, J = 4.6 Hz), 62.3 (d, J = 17.0 Hz), 52.54, 52.51 (d, J = 17.8 Hz), 15.2 (d, J = 7.1 Hz), 12.7 ppm; HRMS calcd for $C_{26}H_{25}FN_2O_6SNa$ [M + Na^+] 535.1310, found 535.1334 (4.6 ppm).

*(+)-1-((2R,3S,4S,5S)-3-Fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**35**).* To a solution of **34** (0.39 g, 0.88 mmol, 1.0 equiv) in MeOH (5.8 mL, 0.13 M) at 0 °C was added NaOMe (86 μL, 0.38 mmol, 0.5 equiv, 25 wt % solution in MeOH). The reaction was stirred for 16 h at 25 °C. Formic acid (~2 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (isopropyl alcohol/DCM, 5:95) provided **35** (0.17 g, 75%): R_f = 0.10 (isopropyl alcohol/DCM, 5:95); $[\alpha]_D^{25}$ +139 (c 1.1, $CDCl_3$); $C_{12}H_{17}FN_2O_4S$; MW = 304.3364 g/mol; IR (neat) ν_{max} 3398, 2884, 2811, 1686 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.96 (s, 1H), 6.47 (dd, J = 25.3, 4.0 Hz, 1H), 4.89 (dd, J = 52.5, 4.1 Hz, 1H), 3.90 (ddd, J = 11.1, 4.8, 0.8 Hz, 1H), 3.74−3.68 (m, 1H), 3.62 (d, J = 11.2 Hz, 1H), 3.52 (dd, J = 11.2, 2.3 Hz, 1H), 3.29 (dd, J = 10.2, 4.8 Hz, 1H), 1.91 (d, J = 1.2 Hz, 3H), 1.23 (d, J = 1.7 Hz, 3H) ppm *OH and NH signals missing possibly due to exchange in CD_3OD*; ^{13}C NMR (125 MHz, acetone-d_6) δ 164.1, 151.9, 139.6 (d, J = 5.2 Hz), 109.8, 100.1 (d, J = 187.4 Hz), 67.8 (d, J = 9.7 Hz), 64.9 (d, J = 3.5 Hz), 62.2 (d, J = 16.8 Hz), 57.6, 54.2 (d, J = 15.9 Hz), 14.6 (d, J = 7.7 Hz), 12.7 ppm; HRMS calcd for $C_{12}H_{17}FN_2O_4SNa$ [M + Na^+] 327.0785, found 327.0778 (−2.34 ppm). The assignment of **35** is supported by an X-ray crystallographic structure (see Supporting Information).

*Synthesis of Novel D-1′,2′-trans-Furanosides through an O4′−C1 Cyclization (Scheme 9). (3S,4S)-4-Hydroxy-3-methyldihydrofuran-2(3H)-one (**S13**).* To LiHMDS (202 mL, 202 mmol, 2.2 equiv, 1 M THF) at −78 °C was added a solution of commerically available (*S*)-β-hydroxy-γ-butyrolactone (9.4 g, 91.7 mmol, 1.0 equiv) in anhydrous THF (150 mL, 0.61 M). Stirring was maintained for 10 min at −78 °C and for 2 h at −40 °C. Upon cooling to −78 °C, MeI (7.4 mL, 119 mmol, 1.3 equiv) as a solution in anhydrous THF (50 mL, 2.4 M) was added and stirred for 2.5 h at −40 °C. The reaction was quenched with formic acid (10 mL) and warmed to 25 °C with stirring for 16 h. Concentration of the reaction mixture was followed by passing it through a silica pad made of 100% EtOAc and reconcentrating. PPTS (2.28 g) was added to the crude mixture dissolved in MeOH (100 mL) to remove the TMS protecting group with stirring for 2 h at 25 °C followed by evaporation. Purification by flash chromatography (hexanes/EtOAc, 20:80) provided the known compound **S13** (8.5 g, 80%). ^{1}H NMR spectroscopic data correlate with the previously reported data:[46] R_f = 0.36 (hexanes/EtOAc, 20:80); $C_5H_8O_3$; MW = 116.1152 g/mol; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (dd, J = 9.6, 6.0 Hz, 1H), 4.27 (appq, J = 5.5 Hz, 1H), 4.07 (dd, J = 9.6, 5.3 Hz, 1H), 2.56 (qd, J = 7.4, 5.7 Hz, 1H), 2.47 (s, 1H), 1.30 (d, J = 7.4 Hz, 3H) ppm.

*(−)-(3S,4S)-3-Allyl-4-hydroxy-3-methyldihydrofuran-2(3H)-one (**S14**).* To a solution of DIPA (6.4 mL, 45.3 mmol, 2.5 equiv) in anhydrous THF (45 mL, 1.0 M) at −78 °C was added *n*-BuLi (18.2 mL, 45.3 mmol, 2.5 equiv, 2.5 M solution in hexanes). The reaction mixture was stirred at 25 °C for 30 min. Upon cooling to −40 °C, **S13** (2.1 g, 18.1 mmol, 1.0 equiv) as a solution in anhydrous THF (36 mL, 0.5 M) was added and stirred for 2 h at −40 °C. A solution of allyl bromide (2.5 mL, 29 mmol, 1.6 equiv) and DMI (4.4 mL, 40 mmol, 2.2 equiv) in anhydrous THF (36 mL, 0.80 M) was added with stirring for 2 h at −35 °C. The reaction mixture was quenched with 6 N HCl (10 mL) and concentrated. The aqueous layer was extracted with isopropyl acetate (4 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 20:80) provided **S14** (1.84 g, 65%): R_f = 0.45 (hexanes/EtOAc, 20:80); $[\alpha]_D^{25}$ −12 (c = 1.0, DCM); $C_8H_{12}O_3$; MW = 156.1791 g/mol; IR (neat) ν_{max} 3456, 3079, 2979, 2931, 1756, 1641 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83−5.72 (m, 1H), 5.21−5.14 (m, 2H), 4.47−4.34 (m, 2H), 4.06 (dd, J = 9.8, 4.4 Hz, 1H), 2.37−2.27 (m, 2H), 1.23 (s, 3H) ppm, *OH signal missing possibly due to exchange in $CDCl_3$*; ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.8, 132.3, 120.0, 72.9, 72.0, 47.2, 40.5, 15.8 ppm; HRMS calcd for $C_8H_{12}O_3Na$ [M + Na^+] 179.0679, found 179.0677 (−0.88 ppm).

*(+)-(2S,3R)-3-Allyl-3-methylbutane-1,2,4-triol (**S15**).* To a solution of **S14** (1.76 g, 11.3 mmol, 1.0 equiv) in anhydrous THF (38 mL, 0.30 M) at 0 °C was added $LiAlH_4$ (17 mL, 16.9 mmol, 1.5 equiv, 1 M solution in THF). The reaction was stirred for 3.5 h at 10 °C, quenched with $Na_2SO_4{\cdot}10H_2O$ (8.5 g), and stirred for an additional 1.5 h at 25 °C. After dilution with EtOAc, the mixture was dried over Na_2SO_4, washed with THF (3 × 20 mL), filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **S15** (1.4 g, 78%): R_f = 0.20 (hexanes/EtOAc, 0:100); $[\alpha]_D^{25}$ +5 (c 2.5, DCM); $C_8H_{16}O_3$; MW = 160.2108 g/mol; IR (neat) ν_{max} 3371, 3076, 2934, 1631 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85−5.71 (m, 1H), 5.09−5.06 (m, 1H), 5.05 (s, 1H), 4.13 (brs, 3H), 3.75−3.60 (m, 2H), 3.58 (apps, 1H), 3.45 (appq, J = 11.1 Hz, 2H), 2.24 (dd, J = 13.8, 7.0 Hz, 1H), 1.94 (dd, J = 13.7, 7.7 Hz, 1H), 0.87 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 118.2, 78.0, 67.8, 62.6, 40.8, 37.6, 19.4 ppm; HRMS calcd for $C_8H_{16}O_3Na$ [M + Na^+] 183.0992, found 183.0987 (−2.5 ppm).

DOI: 10.1021/acs.joc.6b01845
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*(+)-(2R,3S)-2-Allyl-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**S16**).* To a solution of **S15** (3.8 g, 23.8 mmol, 1.0 equiv) in anhydrous DCM (30 mL, 0.80 M) at −40 °C was added NEt_3 (27 mL, 191 mmol, 8.0 equiv) followed by stirring for 30 min. BzCl (6.1 mL, 52.5 mmol, 2.2 equiv) was added, and the reaction mixture was placed at −20 °C for 16 h. The reaction was quenched with 1 N HCl solution (20 mL), and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **S16** (6.6 g, 75%): R_f = 0.44 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +3 (*c* 1.0, DCM); $C_{22}H_{24}O_5$; MW = 368.4230 g/mol; IR (neat) ν_{max} 3510, 3071, 2968, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08−8.01 (m, 4H), 7.61−7.53 (m, 2H), 7.47−7.40 (m, 4H), 5.96−5.86 (m, 1H), 5.16 (d, *J* = 6.1 Hz, 1H), 5.13 (s, 1H), 4.64 (dd, *J* = 11.5, 2.5 Hz, 1H), 4.43 (dd, *J* = 11.5, 8.6 Hz, 1H), 4.41 (d, *J* = 11.3 Hz, 1H), 4.23 (d, *J* = 11.3 Hz, 1H), 4.00 (dd, *J* = 8.6, 2.5 Hz, 1H), 2.73 (brs, 1H), 2.45 (dd, *J* = 13.9, 7.7 Hz, 1H), 2.29 (dd, *J* = 13.9, 7.4 Hz, 1H), 1.14 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.7, 133.5, 133.31, 133.26, 130.1, 129.9, 129.8, 129.7, 128.6, 128.5, 119.0, 73.8, 68.5, 66.7, 41.0, 38.6, 19.0 ppm; HRMS calcd for $C_{22}H_{24}O_5Na$ [M + Na^+] 391.1516, found 391.1520 (1.12 ppm).

*(+)-(2R,3S)-2-Allyl-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl Dibenzoate (**S17**).* To a solution of **S16** (6.7 g, 18.1 mmol, 1.0 equiv) in anhydrous DCM (40 mL, 0.50 M) at 0 °C were added 2,6-lutidine (5.3 mL, 45.2 mmol, 2.5 equiv) and TBSOTf (6.3 mL, 27.1 mmol, 1.5 equiv) The reaction mixture was stirred at 25 °C for 3 h. A saturated solution of NH_4Cl (10 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **S17** (8.4 g, 96%): R_f = 0.63 (hexanes/EtOAc, 80:20); $[\alpha]_D^{25}$ +15 (*c* 2.2, DCM); $C_{28}H_{38}O_5Si$; MW = 482.6838 g/mol; IR (neat) ν_{max} 2975, 2932, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04−8.01 (m, 4H), 7.58−7.53 (m, 2H), 7.47−7.40 (m, 4H), 5.94−5.84 (m, 1H), 5.11 (s, 1H), 5.08 (d, *J* = 7.0 Hz, 1H), 4.66 (dd, *J* = 11.8, 3.5 Hz, 1H), 4.35 (dd, *J* = 11.8, 6.0 Hz, 1H), 4.29 (d, *J* = 11.1 Hz, 1H), 4.24 (d, *J* = 11.1 Hz, 1H), 4.09 (dd, *J* = 5.9, 3.5 Hz, 1H), 2.41 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.29 (dd, *J* = 14.0, 7.8 Hz, 1H), 1.11 (s, 3H), 0.89 (s, 9H), 0.08 (s,3H), 0.08 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.5, 133.8, 133.2, 133.1, 130.4, 130.1, 129.8, 129.6, 128.6, 128.5, 118.6, 74.8, 68.4, 67.6, 41.8, 38.8, 26.1, 19.5, 18.4, −3.8, −4.8 ppm; HRMS calcd for $C_{28}H_{38}O_5SiNa$ [M + Na^+] 505.2381, found 505.2377 (−0.81 ppm).

*(+)-(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2-methyl-2-(2-oxoethyl)butane-1,4-diyl Dibenzoate (**36**).* To a solution of **S17** (8.7 g, 18.1 mmol, 1.0 equiv) in DCM (200 mL, 0.09 M) at −78 °C was bubbled O_3 under vacuum until the solution turned pale blue (about 45 min). The reaction was then purged with nitrogen to remove excess ozone. After addition of NEt_3 (18 mL, 126 mmol, 7.0 equiv), the reaction was warmed to 25 °C for 3 h and concentrated. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **36** (8.4 g, 96%): R_f = 0.66 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +5 (*c* 0.8, DCM); $C_{27}H_{36}O_6Si$; MW = 484.6566 g/mol; IR (neat) ν_{max} 2956, 2930, 1721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.93 (t, *J* = 2.7 Hz, 1H), 8.05−7.99 (m, 4H), 7.60−7.55 (m, 2H), 7.45 (td, *J* = 7.8, 3.9 Hz, 4H), 4.62 (dd, *J* = 12.0, 4.1 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.41 (d, *J* = 11.1 Hz, 1H), 4.38 (dd, *J* = 12.0, 5.1 Hz, 1H), 4.17 (t, *J* = 4.6 Hz, 1H), 2.72 (dd, *J* = 15.5, 3.1 Hz, 1H), 2.55 (dd, *J* = 15.5, 2.3 Hz, 1H), 1.28 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 166.6, 166.3, 133.4, 133.3, 130.0, 129.84, 129.81, 129.7, 128.68, 128.65, 74.3, 68.7, 66.7, 48.2, 42.7, 26.0, 20.4, 18.4, −4.0, −4.8 ppm; HRMS calcd for $C_{27}H_{36}O_6SiNa$ [M + Na^+] 507.2173, found 507.2178 (0.92 ppm).

*(−)-(2R,3S)-2-((R)-2,2-Bis(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl Dibenzoate (**37**).* To the (*R*)-imidazolidinone catalyst (0.29 g, 1.3 mmol, 1.05 equiv) at −40 °C was added **36** (0.60 g, 1.2 mmol, 1.0 equiv) as a solution in anhydrous DMF (1.3 mL, 1.0 M). After being stirred for 10 min, NFSI (0.40 g, 1.3 mmol, 1.02 equiv) was added. Once homogeneous, it was left at 0 °C for 72 h. The reaction mixture was diluted with Et_2O and water (1.0 mL) and treated with Me_2S (0.20 mL, 2.5 mmol, 2.0 equiv). The aqueous layer was extracted with Et_2O (3 × 3 mL), and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. ^1H NMR spectroscopic analysis of the unpurified C2−F aldehyde indicated ∼17:1 diastereomeric ratio for the fluorination. To the crude C2−F aldehyde in anhydrous DCM (12.5 mL, 0.10 M) at −60 °C were added *t*BuSH (0.60 mL, 4.97 mmol, 4.0 equiv) and $BF_3{\cdot}OEt_2$ (0.40 mL, 3.1 mmol, 2.5 equiv). The reaction was stirred at −60 °C for 5 h. Upon addition of NEt_3 (3.5 mL, 24.9 mmol, 20 equiv), stirring at −60 °C was maintained for 15 min. A saturated solution (5 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **37** (0.51 g, 62% for two steps): R_f = 0.39 (hexanes/EtOAc, 90:10); $[\alpha]_D^{25}$ −17 (*c* 1.0, DCM); $C_{35}H_{53}FO_5S_2Si$; MW = 665.0062 g/mol; IR (neat) ν_{max} 2959, 2929, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10−8.02 (m, 4H), 7.60−7.55 (m, 2H), 7.49−7.42 (m, 4H), 5.25 (dd, *J* = 44.5, 2.5 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 10.4 Hz, 1H), 4.43−4.31 (m, 3H), 4.24 (dd, *J* = 26.1, 2.4 Hz, 1H), 1.462 (s, 9H), 1.456 (s, 3H), 1.43 (s, 9H), 0.84 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 166.5, 133.3, 133.1, 130.4, 130.1, 129.8, 129.7, 128.7, 128.5, 95.4 (d, *J* = 183.3 Hz), 74.9, 68.7 (d, *J* = 9.6 Hz), 66.2 (d, *J* = 8.9 Hz), 47.6 (d, *J* = 16.2 Hz), 47.4 (d, *J* = 18.9 Hz), 46.0, 45.3, 32.0, 31.9, 26.1, 18.5, 17.1 (d, *J* = 6.8 Hz), −4.3, −4.5 ppm; HRMS calcd for $C_{35}H_{53}FO_5S_2SiNa$ [M + Na^+] 687.2980, found 687.2976 (−0.62 ppm). **C2−F aldehyde (crude)**: ^1H NMR (500 MHz, $CDCl_3$) δ 9.82 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.92 (m, 4H), 7.60−7.50 (m, 2H), 7.49−7.34 (m, 4H), 5.00 (dd, *J* = 48.0, 1.3 Hz, 1H), 4.58 (dd, *J* = 13.4, 6.1 Hz, 1H), 4.49−4.39 (m, 4H), 1.31 (d, *J* = 1.6 Hz, 3H), 0.91 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H) ppm.

*(−)-(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2-((1R,2S)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methylbutane-1,4-diyl Dibenzoate (**38**).* Following general procedure A, silylated thymine (0.48 mL, 0.29 mmol, 2.0 equiv of a 0.60 M solution in DCM) and I_2 (75 mg, 0.29 mmol, 2.0 equiv) were added to a solution of **37** (98 mg, 0.15 mmol, 1.0 equiv) in anhydrous THF (1.5 mL, 0.10 M) and stirred at 25 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **38** (75 mg, 73%) as a white foam: R_f = 0.16 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ −42 (*c* 0.97, DCM); $C_{36}H_{49}FN_2O_7SSi$; MW = 700.9324 g/mol; IR (neat) ν_{max} 3180, 2957, 2929, 1696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06−7.98 (m, 4H), 7.94 (s, 1H), 7.65 (s, 1H), 7.60−7.55 (m, 2H), 7.47−7.42 (m, 4H), 6.11 (dd, *J* = 30.5, 1.3 Hz, 1H), 5.11 (dd, *J* = 46.8, 1.3 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 2H), 4.41 (d, *J* = 10.9 Hz, 1H), 4.39−4.34 (m, 1H), 4.34−4.31 (m, 1H), 1.92 (s, 3H), 1.39 (s, 3H), 1.33 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 166.2, 163.2, 150.0, 138.0 (d, *J* = 3.2 Hz), 133.4, 133.3, 130.2, 130.0, 129.74, 129.69, 128.67, 128.60, 111.2, 97.3 (d, *J* = 185.8 Hz), 73.7, 67.7 (d, *J* = 6.4 Hz), 65.0 (d, *J* = 7.5 Hz), 58.7 (d, *J* = 20.2 Hz), 46.5 (d, *J* = 19.2 Hz), 45.5, 31.2, 26.0, 18.4, 16.6 (d, *J* = 6.8 Hz), 12.7, −3.8, −4.8 ppm; HRMS calcd for $C_{36}H_{49}FN_2O_7SSiNa$ [M + Na^+] 723.2906, found 723.2908 (0.26 ppm).

*(−)-(2R,3S)-2-((1R,2S)-2-(tert-Butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**39**).* To a solution of **38** (66 mg, 0.095 mmol, 1.0 equiv) in anhydrous THF (0.95 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.40 mL, 4 mL/mmol, ∼70% HF). The reaction was stirred for 96 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **39** (37 mg, 66%): R_f = 0.39 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −26 (*c* 1.3, $CDCl_3$); $C_{30}H_{35}FN_2O_7S$; MW = 586.6715 g/mol; IR (neat) ν_{max} 3446, 3202,

DOI: 10.1021/acs.joc.6b01845
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2962, 1718 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.07−8.03 (m, 4H), 7.71 (s, 1H), 7.60−7.53 (m, 2H), 7.48−7.38 (m, 4H), 6.45 (appd, J = 31.2 Hz, 1H), 4.96 (appd, J = 46.4 Hz, 1H), 4.78 (d, J = 11.5 Hz, 1H), 4.69 (dd, J = 11.6, 2.3 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.47 (dd, J = 11.2, 8.7 Hz, 1H), 4.27−4.22 (m, 1H), 3.65 (d, J = 3.8 Hz, 1H), 1.95 (s, 3H), 1.35 (s, 3H), 1.32 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.7, 163.5, 150.9, 137.9 (d, J = 2.8 Hz), 133.43, 133.35, 129.91, 129.89, 129.83, 128.68, 128.64, 128.5, 111.8, 99.8 (d, J = 184.8 Hz), 72.7 (d, J = 3.2 Hz), 66.5 (d, J = 3.7 Hz), 65.7 (d, J = 3.2 Hz), 58.8 (d, J = 20.0 Hz), 45.6 (d, J = 17.8 Hz), 45.4, 31.1, 16.2 (d, J = 6.2 Hz), 12.8 ppm; HRMS calcd for $C_{30}H_{35}FN_2O_7SNa$ [M + Na^+] 609.2041, found 609.2056 (−2.48 ppm).

*(+)-((2S,3R,4R,5R)-4-Fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2,3-diyl)bis(methylene) Dibenzoate (**40**).* To a solution of **39** (91 mg, 0.16 mmol, 1.0 equiv) in anhydrous THF (1.6 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (61 mg, 0.31 mmol, 2.0 equiv). The reaction was stirred for 4 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **40** (63 mg, 82%): R_f = 0.24 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +11 (c 1.3, DCM); $C_{26}H_{25}FN_2O_7$; MW = 496.4843 g/mol; IR (neat) ν_{max} 3193, 3062,1718, 1692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.09−8.02 (m, 4H), 7.63−7.57 (m, 2H), 7.51−7.44 (m, 4H), 7.40 (s, 1H), 5.96 (dd, J = 18.6, 2.5 Hz, 1H), 5.07 (dd, J = 51.5, 2.5 Hz, 1H), 4.66 (d, J = 5.1 Hz, 2H), 4.61 (appt, J = 5.0 Hz, 1H), 4.55 (dd, J = 11.3, 1.2 Hz, 1H), 4.50 (dd, J = 11.4, 2.3 Hz, 1H), 1.83 (s, 3H), 1.28 (d, J = 1.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 166.2, 163.3, 150.2, 134.6, 133.8, 133.6, 129.83, 129.79, 129.5, 129.4, 128.83, 128.78, 111.5, 100.2 (d, J = 192.8 Hz), 90.0 (d, J = 37.7 Hz), 81.9, 65.6 (d, J = 12.2 Hz), 63.4, 46.6 (d, J = 16.4 Hz), 16.1 (d, J = 4.0 Hz), 12.6 ppm; HRMS calcd for $C_{26}H_{25}FN_2O_7Na$ [M + Na^+] 519.1538, found 519.1537 (−0.19 ppm).

*(+)-1-((2R,3R,4R,5S)-3-Fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**41**).* To a solution of **40** (68 mg, 0.14 mmol, 1.0 equiv) in MeOH (1.0 mL, 0.13 M) at 0 °C was added NaOMe (20 μL, 0.07 mmol, 0.5 equiv, 25 wt % solution in MeOH). The reaction was stirred for 16 h at 25 °C. Formic acid (∼2 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **41** (33 mg, 83%): R_f = 0.13 (hexanes/EtOAc, 0:100); $[\alpha]_D^{25}$ +4 (c 0.8, CD_3OD); $C_{12}H_{17}FN_2O_5$; MW = 288.2722 g/mol; IR (neat) ν_{max} 3363, 2936,1694 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.92 (s, 1H), 6.06 (dd, J = 17.1, 4.2 Hz, 1H), 4.97 (dd, J = 53.1, 4.2 Hz, 1H), 4.18 (appt, J = 4.1 Hz, 1H), 3.82 (dd, J = 11.9, 3.7 Hz, 1H), 3.74 (dd, J = 12.0, 4.6 Hz, 1H), 3.70 (dd, J = 11.0, 1.5 Hz, 1H), 3.62 (dd, J = 11.1, 2.0 Hz, 1H), 1.90 (s, 3H), 1.13 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD; ^{13}C NMR (125 MHz, CD_3OD) δ 166.3, 152.6, 137.7, 111.7, 101.4 (d, J = 189.8 Hz), 89.2 (d, J = 35.9 Hz), 85.8 (d, J = 3.4 Hz), 65.0 (d, J = 12.1 Hz), 62.4, 15.7 (d, J = 2.3 Hz), 12.5 ppm *one carbon missing due to same chemical shift as* CD_3OD; ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 163.7, 150.7, 135.7, 109.7, 99.4 (d, J = 189.1 Hz), 85.9 (d, J = 34.6 Hz), 83.7 (d, J = 3.4 Hz), 63.3 (d, J = 11.3 Hz), 60.9, 46.6 (d, J = 15.9 Hz), 15.4 (d, J = 1.2 Hz), 12.3 ppm; HRMS calcd for $C_{12}H_{17}FN_2O_5Na$ [M + Na^+] 311.1014, found 311.1018 (1.53 ppm).

*Synthesis of Novel L-1′,2′-cis-Thiofuranosides through S1′−C4 Cyclization (Scheme 10). (−)-(2R,3S)-2-((1R,2S)-2-(tert-Butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl Dibenzoate (**S18**).* To a solution of **39** (0.10 g, 0.17 mmol, 1.0 equiv) in anhydrous DCM (1.8 mL, 0.10 M) at 0 °C were added triethylamine (40 μL, 0.26 mmol, 1.5 equiv) and methanesulfonyl chloride (35 μL, 0.43 mmol, 2.5 equiv). The reaction was stirred for 16 h at 25 °C. A 1.0 N solution (0.50 mL) of HCl was added, and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (DCM/acetone, 90:10) provided **S18** (54 mg, 47%): R_f = 0.41 (DCM/acetone, 90:10); $[\alpha]_D^{25}$ −31 (c 1.6, $CDCl_3$); $C_{31}H_{37}FN_2O_9S_2$; MW = 664.7619 g/mol; IR (neat) ν_{max} 3186, 3066, 2965, 1712, 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.11−8.03 (m, 4H), 7.67 (s, 1H), 7.61−7.56 (m, 2H), 7.50−7.42 (m, 4H), 6.28 (appd, J = 31.7 Hz, 1H), 5.69 (appd, J = 8.2 Hz, 1H), 4.95 (d, J = 46.6 Hz, 1H), 4.90 (dd, J = 12.5, 1.3 Hz, 1H), 4.69 (d, J = 11.3 Hz, 1H), 4.57 (dd, J = 12.6, 8.7 Hz, 1H), 4.51 (d, J = 11.3 Hz, 1H), 3.09 (s, 3H), 1.92 (s, 3H), 1.49 (s, 3H), 1.35 (s, 9H) ppm contains ∼5% of cyclized product ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.166, 166.157, 163.4, 150.4, 137.6 (d, J = 2.7 Hz), 133.7, 133.6, 129.91, 129.89, 129.52, 129.45, 128.8, 128.7, 111.7, 98.8 (d, J = 187.6 Hz), 82.2, 64.5 (d, J = 7.5 Hz), 64.3 (d, J = 4.9 Hz), 58.2 (d, J = 19.9 Hz), 45.9, 45.5 (d, J = 18.1 Hz), 39.5, 31.1, 18.1 (d, J = 6.3 Hz), 12.8 ppm; HRMS calcd for $C_{31}H_{37}FN_2O_9S_2Na$ [M + Na^+] 687.1817, found 687.1828 (1.6 ppm).

*(−)-((2R,3S,4R,5S)-4-Fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrothiophene-2,3-diyl)bis-(methylene) Dibenzoate (**S19**).* A solution of **S18** (0.20 g, 0.30 mmol, 1.0 equiv) in 2,6-lutidine (30 mL, 0.01 M) was refluxed for 3 h at 160 °C. A 1.0 N solution (5.0 mL) of HCl was added, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 30:70) provided **S19** (0.14 g, 92%): R_f = 0.51 (hexanes/EtOAc, 30:70); $[\alpha]_D^{25}$ −74 (c 2.0, $CDCl_3$); $C_{26}H_{25}FN_2O_6S$; MW = 512.5499 g/mol; IR (neat) ν_{max} 3188, 3070, 2979, 1723, 1686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.08−7.99 (m, 4H), 7.79 (s, 1H), 7.62−7.55 (m, 2H), 7.48−7.42 (m, 4H), 6.61 (dd, J = 25.5, 3.8 Hz, 1H), 5.03 (dd, J = 52.6, 3.8 Hz, 1H), 4.93−4.86 (m, 1H), 4.70 (d, J = 11.2 Hz, 1H), 4.65 (dd, J = 11.4, 6.6 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 3.73 (dd, J = 8.5, 6.7 Hz, 1H), 1.96 (s, 3H), 1.47 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 166.1, 163.3, 151.1, 138.7 (d, J = 4.8 Hz), 133.63, 133.58, 129.9, 129.8, 129.6, 129.4, 128.73, 128.69, 110.8, 98.7 (d, J = 191.8 Hz), 65.4 (d, J = 6.0 Hz), 64.7 (d, J = 7.5 Hz), 62.3 (d, J = 16.7 Hz), 55.4, 51.7 (d, J = 15.6 Hz), 21.4 (d, J = 7.7 Hz), 12.7 ppm; HRMS calcd for $C_{26}H_{25}FN_2O_6SNa$ [M + Na^+] 535.1310, found 535.1309 (−0.11 ppm).

*(−)-1-((2S,3R,4S,5R)-3-Fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrothiophen-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**42**).* To a solution of **S19** (0.14 g, 0.27 mmol, 1.0 equiv) in MeOH (4.0 mL, 0.07 M) at 0 °C was added NaOMe (30 μL, 0.14 mmol, 0.5 equiv, 25 wt % solution in MeOH). The reaction was stirred for 16 h at 25 °C. Amberlite R (120, H^+) (0.7 g) was added to neutralize the reaction mixture before filtration and concentration. Purification by flash chromatography (isopropyl alcohol/DCM, 20:80) provided **42** (50 mg, 60%): R_f = 0.54 (isopropyl alcohol/DCM, 20:80); $[\alpha]_D^{25}$ −186 (c 1.0, CD_3OD); $C_{12}H_{17}FN_2O_4S$; MW = 304.3378 g/mol; IR (neat) ν_{max} 3427, 2530, 1655 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.90 (s, 1H), 6.44 (dd, J = 25.6, 3.8 Hz, 1H), 4.82 (dd, J = 53.0, 3.8 Hz, 1H), 3.97 (dd, J = 11.0, 5.6 Hz, 1H), 3.73 (d, J = 11.1 Hz, 1H), 3.71−3.62 (m, 2H), 3.30−3.26 (m, 1H), 1.87 (s, 3H), 1.28 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD; ^{13}C NMR (125 MHz, CD_3OD) δ 166.1, 152.8, 140.8 (d, J = 4.6 Hz), 110.5, 100.3 (d, J = 188.9 Hz), 64.4 (d, J = 5.3 Hz), 63.5 (d, J = 16.8 Hz), 62.9 (d, J = 7.7 Hz), 60.9 (d, J = 1.4 Hz), 54.4 (d, J = 15.8 Hz), 21.2 (d, J = 8.6 Hz), 12.4 ppm; HRMS calcd for $C_{12}H_{17}FN_2O_4SNa$ [M + Na^+] 327.0785, found 327.0798 (3.82 ppm).

*Synthesis of Novel D-1′,2′-trans-Furanosides through an O4′−C1 Cyclization (Scheme 11). (−)-(2R,3S)-2-((S)-2,2-Bis(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl Dibenzoate (**43**).* To the (*S*)-imidazolidinone catalyst (1.1 g, 5.1 mmol, 1.05 equiv) at −40 °C was added **36** (2.4 g, 4.9 mmol, 1.0 equiv) as a solution in anhydrous DMF (5.0 mL, 1.0 M). After being stirred for 10 min, NFSI (1.6 g, 4.96 mmol, 1.02 equiv) was added. Once homogeneous, it was left at 0 °C for 72 h. The reaction mixture was diluted with Et_2O and water (3.0 mL) and treated with Me_2S (0.70 mL, 9.7 mmol, 2.0 equiv). The aqueous layer was extracted with Et_2O (3 × 5 mL), and the combined organic layers were washed with 1 N HCl (to remove the catalyst), a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. ^1H NMR

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

spectroscopic analysis of the unpurified C2−F aldehyde indicated ~17:1 diastereomeric ratio for the fluorination. To the crude C2−F aldehyde in anhydrous DCM (50 mL, 0.10 M) at −60 °C were added *t*BuSH (2.2 mL, 19.5 mmol, 4.0 equiv) and $BF_3{\cdot}OEt_2$ (1.6 mL, 12.2 mmol, 2.5 equiv). The reaction was stirred at −60 °C for 5 h. Upon addition of NEt_3 (14 mL, 97.3 mmol, 20 equiv), stirring at −60 °C was maintained for 15 min. A saturated solution (10 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **43** (2.2 g, 68% for two steps): R_f = 0.37 (hexanes/EtOAc, 90:10); $[\alpha]_D^{25}$ −61 (*c* 1.2, DCM); $C_{35}H_{53}FO_5S_2Si$; MW = 665.0062 g/mol; IR (neat) ν_{max} 2958, 2928, 1721 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98−7.90 (m, 4H), 7.53−7.48 (m, 2H), 7.41−7.31 (m, 4H), 5.12 (dd, *J* = 43.8, 1.6 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.63−4.57 (m, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.44−4.40 (m, 1H), 4.36 (dd, *J* = 26.1, 1.9 Hz, 1H), 1.42 (s, 9H), 1.39 (s, 9H), 1.23 (s, 3H), 0.89 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 166.5, 133.1, 132.9, 130.4, 129.9, 129.74, 129.68, 128.44, 128.43, 98.9 (d, *J* = 186.4 Hz), 71.2 (d, *J* = 6.0 Hz), 67.2, 65.6 (d, *J* = 1.2 Hz), 46.7 (d, *J* = 17.7 Hz), 46.5 (d, *J* = 22.7 Hz), 46.2, 44.7, 32.0, 31.6, 26.1, 18.4, 15.5 (d, *J* = 6.4 Hz), −4.3, −4.6 (d, *J* = 1.9 Hz) ppm; HRMS calcd for $C_{35}H_{53}FO_5S_2SiNa$ [M + Na^+] 687.2980, found 687.2974 (−0.90 ppm). **C2−F aldehyde** (crude): ^1H NMR (500 MHz, $CDCl_3$) δ 9.85 (dd, *J* = 6.6, 1.5 Hz, 1H), 8.07−7.96 (m, 4H), 7.61−7.53 (m, 2H), 7.46 (m, 4H), 4.81 (dd, *J* = 47.7, 1.5 Hz, 1H), 4.65 (dd, *J* = 12.1, 4.0 Hz, 1H), 4.48 (d, *J* = 11.5 Hz, 1H), 4.45−4.38 (m, 2H), 4.21 (dt, *J* = 11.9, 6.0 Hz, 1H), 1.33 (d, *J* = 1.5 Hz, 3H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H) ppm.

*(+)-(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2-((1S,2R)-2-(tert-butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-2-methylbutane-1,4-diyl Dibenzoate (**44**).* Following general procedure A, silylated thymine (0.51 mL, 0.32 mmol, 2.0 equiv of a 0.60 M solution in DCM) and I_2 (80 mg, 0.32 mmol, 2.0 equiv) were added to a solution of **43** (0.11 g, 0.16 mmol, 1.0 equiv) in anhydrous THF (1.6 mL, 0.10 M) and stirred at 25 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **44** (81 mg, 73%) as a white foam: R_f = 0.27 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +71 (*c* 1.1, DCM); $C_{36}H_{49}FN_2O_7SSi$; MW = 700.9324 g/mol; IR (neat) ν_{max} 3185, 2958, 2930, 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.00−7.86 (m, 4H), 7.68 (s, 1H), 7.57−7.45 (m, 2H), 7.45−7.37 (m, 2H), 7.35−7.30 (m, 2H), 6.19 (appd, *J* = 29.6 Hz, 1H), 4.90 (appd, *J* = 46.0 Hz, 1H), 4.70 (d, *J* = 12.2 Hz, 1H), 4.57 (dd, *J* = 11.6, 4.2 Hz, 1H), 4.53−4.49 (m, 2H), 4.45 (dd, *J* = 11.6, 5.0 Hz, 1H), 1.96 (s, 3H), 1.29 (s, 9H), 1.24 (s, 3H), 0.84 (s, 9H), 0.13 (s, 3H), 0.09 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 166.2, 163.4, 150.1, 137.7 (d, *J* = 2.6 Hz), 133.2, 133.0, 130.3, 129.9, 129.70, 129.66, 128.52, 128.46, 111.6, 99.7 (d, *J* = 188.0 Hz), 70.9 (d, *J* = 5.5 Hz), 66.6, 64.9, 58.4 (d, *J* = 20.1 Hz), 45.6 (d, *J* = 16.5 Hz), 45.0 (d, *J* = 0.8 Hz), 31.0, 25.9, 18.4, 14.3 (d, *J* = 6.6 Hz), 12.6, −4.0, −5.3 (d, *J* = 1.8 Hz) ppm; HRMS calcd for $C_{36}H_{49}FN_2O_7SSiNa$ [M + Na^+] 723.2906, found 723.2905 (−0.17 ppm).

*(+)-(2R,3S)-2-((1S,2R)-2-(tert-Butylthio)-1-fluoro-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)ethyl)-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**S20**).* To a solution of **44** (71 mg, 0.10 mmol, 1.0 equiv) in anhydrous THF (1.0 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.40 mL, 4 mL/mmol, ~70% HF). The reaction was stirred for 72 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **S20** (40 mg, 68%): R_f = 0.29 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +44 (*c* 1.1, $CDCl_3$); $C_{30}H_{35}FN_2O_7S$; MW = 586.6715 g/mol; IR (neat) ν_{max} 3468, 3172, 2963, 1686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.01−7.97 (m, 4H), 7.73 (s, 1H), 7.58−7.51 (m, 2H), 7.45−7.37 (m, 4H), 6.52 (appd, *J* = 31.1 Hz, 1H), 4.89 (appd, *J* = 46.2 Hz, 1H), 4.65 (dd, *J* = 11.7, 3.5 Hz, 2H), 4.51 (dd, *J* = 11.6, 7.6 Hz, 1H), 4.43−4.35 (m, 2H), 3.20 (d, *J* = 5.0 Hz, 1H), 1.96 (s, 3H), 1.31 (s, 12H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.2, 163.7, 150.6, 137.9 (d, *J* = 2.1 Hz), 133.5, 133.3, 129.9, 129.84, 129.77, 129.6, 128.7, 128.6, 111.7, 100.4 (d, *J* = 187.1 Hz), 70.7 (d, *J* = 4.9 Hz), 66.1 (d, *J* = 2.1 Hz), 65.6 (d, *J* = 5.0 Hz), 59.3 (d, *J* = 20.1 Hz), 45.2, 45.0 (d, *J* = 17.0 Hz), 31.1, 13.7 (d, *J* = 3.9 Hz), 12.8 ppm; HRMS calcd for $C_{30}H_{36}FN_2O_7S$ [M + H^+] 587.2222, found 587.2221 (−0.07 ppm).

*(+)-((2S,3R,4S,5S)-4-Fluoro-3-methyl-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2,3-diyl)bis(methylene) Dibenzoate (**45**).* To a solution of **S20** (0.19 g, 0.33 mmol, 1.0 equiv) in anhydrous THF (3.3 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (0.13 g, 0.65 mmol, 2.0 equiv). The reaction was stirred for 4 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **45** (0.13 g, 78%): R_f = 0.30 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +35 (*c* 1.4, $CDCl_3$); $C_{26}H_{25}FN_2O_7$; MW = 496.4843 g/mol; IR (neat) ν_{max} 3062, 2894,1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.10−8.01 (m, 4H), 7.61−7.54 (m, 2H), 7.49−7.40 (m, 4H), 7.06 (s, 1H), 5.75 (dd, *J* = 24.6, 4.8 Hz, 1H), 5.67 (dd, *J* = 14.5, 4.8 Hz, 1H), 4.89 (dd, *J* = 6.9, 4.6 Hz, 1H), 4.59−4.50 (m, 2H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 1.92 (s, 3H), 1.31 (d, *J* = 3.7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 166.2, 163.7, 150.2, 138.1, 133.6, 133.5, 129.90, 129.87, 129.53, 129.45, 128.7, 128.6, 111.5, 95.9 (d, *J* = 195.0 Hz), 93.0 (d, *J* = 35.0 Hz), 81.9 (d, *J* = 3.7 Hz), 66.7, 63.7, 47.9 (d, *J* = 17.8 Hz), 12.5, 11.6 (d, *J* = 11.7 Hz) ppm; HRMS calcd for $C_{26}H_{25}FN_2O_7Na$ [M + Na^+] 519.1538, found 519.1533 (−0.99 ppm).

*(+)-1-((2S,3S,4R,5S)-3-Fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**46**).* To a solution of **45** (0.11 g, 0.22 mmol, 1.0 equiv) in MeOH (8.0 mL, 0.03 M) was bubbled NH_3. The reaction was stirred for 72 h at 25 °C and concentrated. Purification by flash chromatography (hexanes/EtOAc, 0:100) provided **46** (31.9 mg, 50%): R_f = 0.09 (hexanes/EtOAc, 0:100); $[\alpha]_D^{25}$ +49 (*c* 1.4, CD_3OD); $C_{12}H_{17}FN_2O_5$; MW = 288.2722 g/mol; IR (neat) ν_{max} 3392, 2941,1691 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.50 (s, 1H), 5.97 (dd, *J* = 15.6, 5.0 Hz, 1H), 5.28 (dd, *J* = 54.2, 5.0 Hz, 1H), 4.43−4.39 (m, 1H), 3.74−3.66 (m, 2H), 3.59−3.53 (m, 2H), 1.90 (s, 3H), 1.07 (d, *J* = 3.5 Hz, 3H) ppm *OH signals missing possibly due to exchange in* CD_3OD; ^{13}C NMR (125 MHz, CD_3OD) δ 166.4, 152.5, 138.6, 111.9, 97.9 (d, *J* = 193.0 Hz), 90.8 (d, *J* = 34.7 Hz), 85.7 (d, *J* = 3.7 Hz), 65.9, 62.4 (d, *J* = 0.8 Hz), 49.7 (d, *J* = 16.9 Hz), 12.4, 11.0 (d, *J* = 11.3 Hz) ppm; HRMS calcd for $C_{12}H_{17}FN_2O_5Na$ [M + Na^+] 311.1014, found 311.1012 (−0.71 ppm).

*Synthesis of Nucleoside Analogues with Various Nucleobases (Table 3). (+)-9-((1R,2S,3R,4S)-3,5-Bis(benzyloxy)-4-((tert-butyldimethylsilyl)oxy)-1-(tert-butylthio)-2-fluoropentyl)-6-chloro-9H-purine (**47**).* To a solution of **12** (0.44 g, 0.73 mmol, 1.0 equiv) in anhydrous THF (7.3 mL, 0.10 M) at 0 °C were added 6-Cl-purine (0.40 g, 2.55 mmol, 3.5 equiv) and I_2 (0.37 g, 1.46 mmol, 2.0 equiv). The reaction mixture was stirred at 25 °C for 16 h. A saturated solution (5 mL) of $Na_2S_2O_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 7 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. ^1H NMR spectroscopic analysis of the unpurified product indicated a 3:1 mixture of the 1,2-*syn* diastereoisomer **47** with the corresponding aldehyde. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereoisomer **47**. The minor 1,2-*anti* diastereoisomer has yet to be identified. Purification by flash chromatography (hexanes/EtOAc, 90:10) did not allow separation of the thioaminal from the aldehyde, providing 0.28 g of a 3:1 mixture of **47** and the corresponding aldehyde that was used in the next step. Isolation of **47** and its full characterization were done from recovered starting material in the following TBS deprotection step.

47: R_f = 0.19 (hexanes/EtOAc, 90:10); $[\alpha]_D^{25}$ +41 (*c* 0.3, $CDCl_3$); $C_{34}H_{46}ClFN_4O_3SSi$; MW = 673.3604 g/mol; IR (neat) ν_{max} 2958,

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

2925, 2850, 1556 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.22 (s, 1H), 7.39−7.26 (m, 10H), 6.08 (dd, J = 16.0, 5.9 Hz, 1H), 5.24−5.12 (m, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.55 (d, J = 11.5 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 4.16 (appdt, J = 7.9, 4.0 Hz, 1H), 3.67 (dd, J = 10.0, 3.5 Hz, 1H), 3.56 (appdt, J = 23.3, 4.0 Hz, 1H), 3.49 (ddd, J = 10.1, 6.7, 3.6 Hz, 1H), 1.21 (s, 9H), 0.78 (s, 9H), 0.03 (s, 3H), −0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2, 151.4, 151.1, 145.4, 138.3, 137.8, 131.6, 128.7, 128.4, 128.2, 128.1, 127.68, 127.65, 91.8 (d, J = 186.5 Hz), 78.1 (d, J = 16.6 Hz), 73.8, 73.3, 71.6 (d, J = 4.9 Hz), 71.0, 57.7 (d, J = 25.7 Hz), 45.5, 31.0, 25.9, 18.2, −4.0, −4.7 ppm; HRMS calcd for $C_{34}H_{46}ClFN_4O_3SSiNa$ [M + Na^+] 695.2625, found 695.2631 (0.95 ppm).

*(+)-(2S,3R,4S,5R)-1,3-Bis(benzyloxy)-5-(tert-butylthio)-5-(6-chloro-9H-purin-9-yl)-4-fluoropentan-2-ol (**S21**).* To a solution of a 3:1 mixture of **47** and the corresponding aldehyde (75 mg, 0.11 mmol, 1.0 equiv) in anhydrous THF (1.2 mL, 0.10 M) in a plastic vial at 0 °C was added trihydrofluoride triethylamine (0.18 mL, 1.1 mmol, 10 equiv). The reaction took 48 h at 25 °C to go to completion with additional trihydrofluoride triethylamine (total of 40 equiv). A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 30:70) provided lactol **S1** (13 mg) which could be separated from **S21** (26.9 mg, 43%): R_f = 0.13 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +90 (c 0.8, $CDCl_3$); $C_{28}H_{32}ClFN_4O_3S$; MW = 559.0974 g/mol; IR (neat) ν_{max} 3355, 2958, 2866, 1583, 1562 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.61 (s, 1H), 7.38−7.27 (m, 10H), 6.25 (dd, J = 28.9, 2.0 Hz, 1H), 5.04 (ddd, J = 48.8, 7.7, 2.0 Hz, 1H), 4.79 (d, J = 11.2 Hz, 1H), 4.55 (d, J = 11.1 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.15−4.11 (m, 1H), 4.07 (dd, J = 11.9, 8.0 Hz, 1H), 3.64 (dd, J = 9.1, 6.6 Hz, 1H), 3.51 (dd, J = 9.3, 5.8 Hz, 1H), 2.52 (brs, 1H), 1.19 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 151.4, 151.0, 145.6, 137.9, 137.7, 131.7, 128.63, 128.60, 128.4, 128.2, 128.1, 127.9, 96.7 (d, J = 182.8 Hz), 77.8 (d, J = 17.3 Hz), 75.1 (d, J = 3.5 Hz), 73.7, 70.7, 69.7 (d, J = 7.6 Hz), 57.6 (d, J = 20.2 Hz), 45.3, 31.0 ppm; HRMS calcd for $C_{28}H_{32}ClFN_4O_3SNa$ [M + Na^+] 581.1760, found 581.1779 (3.3 ppm).

*(+)-(2S,3R,4S,5R)-1,3-Bis(benzyloxy)-5-(tert-butylthio)-5-(6-chloro-9H-purin-9-yl)-4-fluoropentan-2-yl Methanesulfonate (**S22**).* To a solution of **S21** (33 mg, 0.06 mmol, 1.0 equiv) in anhydrous DCM (0.20 mL, 0.30 M) at 0 °C were added triethylamine (20 μL, 0.12 mmol, 2.0 equiv) and methanesulfonyl chloride (7 μL, 0.09 mmol, 1.5 equiv). The reaction was stirred for 4 h at 25 °C. Water (0.50 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 1 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **S22** (22.6 mg, 60%): R_f = 0.15 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ +79 (c 1.5, $CDCl_3$); $C_{29}H_{34}ClFN_4O_5S_2$; MW = 637.1824 g/mol; IR (neat) ν_{max} 3022, 2958, 2861, 1588, 1561 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.47 (s, 1H), 7.37−7.25 (m, 10H), 6.23 (dd, J = 23.7, 3.8 Hz, 1H), 5.11−4.98 (m, 2H), 4.72 (d, J = 11.2 Hz, 1H), 4.62 (d, J = 11.2 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.14 (ddd, J = 16.8, 6.0, 3.8 Hz, 1H), 3.90−3.85 (m, 1H), 3.80 (dd, J = 10.6, 4.9 Hz, 1H), 3.14 (s, 3H), 1.23 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1 (d, J = 2.2 Hz), 151.5, 151.0, 145.7, 137.3, 137.1, 131.8, 128.74, 128.68, 128.5, 128.4, 128.2, 127.9, 94.0 (d, J = 185.2 Hz), 78.0 (d, J = 5.8 Hz), 76.7 (d, J = 18.7 Hz), 75.3 (d, J = 2.5 Hz), 73.6, 68.0, 57.1 (d, J = 21.8 Hz), 46.0, 38.8, 31.1 ppm; HRMS calcd for $C_{29}H_{34}ClFN_4O_5S_2Na$ [M + Na^+] 659.1535, found 659.1558 (3.42 ppm).

*(+)-9-((2R,3S,4S,5R)-4-(Benzyloxy)-5-((benzyloxy)methyl)-3-fluorotetrahydrothiophen-2-yl)-6-chloro-9H-purine (**48**).* A solution of **S22** (21 mg, 0.03 mmol, 1.0 equiv) in 2,6-lutidine (1.0 mL, 0.03 M) was refluxed for 4 h at 160 °C. Upon cooling to room temperature, the reaction mixture was concentrated. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **48** (7.0 mg, 45%): R_f = 0.46 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +47 (c 0.6, $CDCl_3$); $C_{24}H_{22}ClFN_4O_2S$; MW = 484.9744 g/mol; IR (neat) ν_{max} 3033, 2866, 1583, 1562 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.75 (s, 1H), 7.41−7.27 (m, 10H), 6.47 (dd, J = 12.0, 4.9 Hz, 1H), 5.21 (appdt, J = 50.6, 5.3 Hz, 1H), 4.66 (d, J = 11.7 Hz, 1H), 4.58 (apps, 2H), 4.54 (d, J = 11.7 Hz, 1H), 4.47 (appdt, J = 10.5, 5.2 Hz, 1H), 3.72−3.64 (m, 3H) ppm; ^{13}C NMR (175 MHz, $CDCl_3$) δ 152.3, 152.2, 151.3, 145.7, 137.4, 136.9, 131.9, 128.768, 128.767, 128.5, 128.31, 128.30, 128.1, 95.4 (d, J = 196.3 Hz), 80.4 (d, J = 22.1 Hz), 73.5, 73.1, 68.9, 58.0 (d, J = 17.5 Hz), 47.8 (d, J = 4.2 Hz) ppm; HRMS calcd for $C_{24}H_{22}ClFN_4O_2SNa$ [M + Na^+] 507.1028, found 507.1034 (1.17 ppm).

*(−)-(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2-((1R,2S)-2-(tert-butylthio)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-1-fluoroethyl)-2-methylbutane-1,4-diyl Dibenzoate (**49**).* Following general procedure A, silylated uracil (1.1 mL, 0.79 mmol, 3.0 equiv of a 0.74 M solution in DCM) and I_2 (0.13 g, 0.53 mmol, 2.0 equiv) were added to a solution of **37** (0.18 g, 0.27 mmol, 1.0 equiv) in anhydrous THF (2.6 mL, 0.10 M) and stirred at 25 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **49** (0.16 g, 86%) as a white foam: R_f = 0.41 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −42 (c 1.3, $CDCl_3$); $C_{35}H_{47}FN_2O_7SSi$; MW = 686.9058 g/mol; IR (neat) ν_{max} 3172, 2963, 2861, 1696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 8.06−7.98 (m, 4H), 7.89 (dd, J = 8.2, 1.9 Hz, 1H), 7.60−7.55 (m, 2H), 7.50−7.42 (m, 4H), 6.08 (dd, J = 31.2, 0.9 Hz, 1H), 5.76 (dd, J = 8.2, 1.7 Hz, 1H), 5.13 (dd, J = 46.8, 1.1 Hz, 1H), 4.66 (d, J = 10.8 Hz, 1H), 4.65 (d, J = 11.9 Hz, 1H), 4.41 (d, J = 10.8 Hz, 1H), 4.36 (dd, J = 6.3, 2.8 Hz, 1H), 4.30 (ddd, J = 11.9, 6.4, 2.5 Hz, 1H), 1.39 (d, J = 1.3 Hz, 3H), 1.33 (s,9), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 166.2, 162.6, 150.0, 142.5 (d, J = 3.0 Hz), 133.4, 133.3, 130.1, 129.9, 129.71, 129.66, 128.7, 128.6, 102.5, 96.9 (d, J = 184.9 Hz), 73.6, 67.6 (d, J = 6.7 Hz), 64.9 (d, J = 7.7 Hz), 59.1 (d, J = 20.1 Hz), 46.4 (d, J = 18.9 Hz), 45.5, 31.1, 26.0, 18.4, 16.4 (d, J = 7.1 Hz), −3.9, −4.9 ppm; HRMS calcd for $C_{35}H_{47}FN_2O_7SSiNa$ [M + Na^+] 709.2749, found 709.2763 (1.94 ppm).

*(−)-(2R,3S)-2-((1R,2S)-2-(tert-Butylthio)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**S23**).* To a solution of **49** (0.10 g, 0.15 mmol, 1.0 equiv) in anhydrous THF (1.5 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (0.45 mL, 3 mL/mmol, ∼70% HF). The reaction was stirred for 96 h at 25 °C. A saturated solution (1.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **S23** (52 mg, 61%): R_f = 0.37 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −26 (c 1.3, $CDCl_3$); $C_{29}H_{33}FN_2O_7S$; MW = 572.6449 g/mol; IR (neat) ν_{max} 3441, 2957, 1691 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (s, 1H), 8.07−8.01 (m, 4H), 7.94 (dd, J = 8.2, 1.6 Hz, 1H), 7.61−7.53 (m, 2H), 7.48−7.40 (m, 4H), 6.45 (appd, J = 31.9 Hz, 1H), 5.80 (d, J = 8.2 Hz, 1H), 4.96 (appd, J = 46.3 Hz, 1H), 4.85 (d, J = 11.5 Hz, 1H), 4.68 (dd, J = 11.6, 2.3 Hz, 1H), 4.53 (d, J = 11.4 Hz, 1H), 4.50−4.45 (m, 1H), 4.24−4.16 (m, 1H), 3.54 (d, J = 3.7 Hz, 1H), 1.36 (d, J = 1.7 Hz, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.8, 162.8, 150.7, 142.4 (d, J = 3.0 Hz), 133.44, 133.41, 129.88, 129.85, 129.823, 129.817, 128.7, 128.6, 102.9, 99.5 (d, J = 185.1 Hz), 72.9 (d, J = 3.0 Hz), 66.4 (d, J = 3.8 Hz), 65.6 (d, J = 4.4 Hz), 59.4 (d, J = 20.0 Hz), 45.6 (d, J = 17.8 Hz), 45.5, 31.1, 16.5 (d, J = 6.0 Hz) ppm; HRMS calcd for $C_{29}H_{33}FN_2O_7SNa$ [M + Na^+] 595.1885, found 595.1890 (0.97 ppm).

*(+)-((2S,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) Dibenzoate (**S24**).* To a solution of **S23** (0.27 g, 0.46 mmol, 1.0 equiv) in anhydrous THF (5.0 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (0.18 g, 0.93 mmol, 2.0 equiv). The reaction was stirred for 4 h at 25 °C. A saturated solution (3.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/

DOI: 10.1021/acs.joc.6b01845
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EtOAc, 30:70) provided **S24** (0.16 g, 73%): R_f = 0.41 (hexanes/EtOAc, 30:70); $[\alpha]_D^{25}$ +38 (*c* 0.7, $CDCl_3$); $C_{25}H_{23}FN_2O_7$; MW = 482.4577 g/mol; IR (neat) ν_{max} 3204, 3054,1712, 1685 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.07−8.02 (m, 4H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.63−7.58 (m, 2H), 7.50−7.45 (m, 4H), 5.91 (dd, *J* = 19.0, 1.8 Hz, 1H), 5.74 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.06 (dd, *J* = 50.9, 1.8 Hz, 1H), 4.72−4.61 (m, 3H), 4.55 (d, *J* = 11.3 Hz, 1H), 4.50 (dd, *J* = 11.3, 2.6 Hz, 1H), 1.23 (d, *J* = 1.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ166.3, 166.2, 162.5, 150.0, 138.8, 133.8, 133.7, 129.83, 129.78, 129.5, 129.3, 128.80, 128.79, 102.8, 100.4 (d, *J* = 192.6 Hz), 90.5 (d, *J* = 38.7 Hz), 82.4, 65.4 (d, *J* = 12.1 Hz), 63.2, 46.7 (d, *J* = 16.5 Hz), 15.8 (d, *J* = 4.5 Hz) ppm; HRMS calcd for $C_{25}H_{23}FN_2O_7Na$ [M + Na^+] 505.1382, found 505.1384 (0.56 ppm).

*(+)-1-((2R,3R,4R,5S)-3-Fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)pyrimidine-2,4(1H,3H)-dione (**50**).* To a solution of **S24** (96 mg, 0.20 mmol, 1.0 equiv) in MeOH (1.6 mL, 0.13 M) at 0 °C was added NaOMe (25 μL, 0.10 mmol, 0.5 equiv, 25 wt % solution in MeOH). The reaction was stirred for 16 h at 25 °C. A 1 N HCl solution (∼10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/MeOH, 95:5) provided **50** (44 mg, 81%): R_f = 0.29 (DCM/MeOH, 95:5); $[\alpha]_D^{25}$ +28 (*c* 1.4, CD_3OD); $C_{11}H_{15}FN_2O_5$; MW = 274.2456 g/mol; IR (neat) ν_{max} 3392, 2941,1686 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 8.07 (d, *J* = 8.2 Hz, 1H), 6.03 (dd, *J* = 17.5, 3.7 Hz, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 4.96 (dd, *J* = 52.7, 3.6 Hz, 1H), 4.19 (appt, *J* = 4.3 Hz, 1H), 3.81 (dd, *J* = 12.0, 3.9 Hz, 1H), 3.75 (dd, *J* = 11.9, 4.9 Hz, 1H), 3.69 (dd, *J* = 11.1, 2.0 Hz, 1H), 3.64 (dd, *J* = 11.1, 2.0 Hz, 1H), 1.10 (d, *J* = 0.7 Hz, 3H) ppm *OH and NH signals missing possibly due to exchange in* CD_3OD; ^{13}C NMR (125 MHz, CD_3CN) δ 163.9, 151.6, 140.9, 102.7, 101.7 (d, *J* = 188.3 Hz), 89.3 (d, *J* = 36.8 Hz), 85.7 (d, *J* = 1.8 Hz), 64.5 (d, *J* = 12.2 Hz), 61.9, 48.2 (d, *J* = 16.2 Hz), 15.4 (d, *J* = 3.4 Hz) ppm; HRMS calcd for $C_{11}H_{15}FN_2O_5Na$ [M + Na^+] 297.0857, found 297.0863 (1.53 ppm).

*(−)-(2R,3S)-2-((1R,2S)-2-(4-Benzamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-3-((tert-butyldimethylsilyl)oxy)-2-methylbutane-1,4-diyl Dibenzoate (**51**).* Following general procedure A, silylated N^4-BzCytosine (3.5 mL, 2.38 mmol, 3.0 equiv of a 0.68 M solution in DCM) and I_2 (0.40 g, 1.6 mmol, 2.0 equiv) were added to a solution of **37** (0.53 g, 0.79 mmol, 1.0 equiv) in anhydrous THF (8.0 mL, 0.10 M) and stirred at 25 °C for 16 h. ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **51** (0.51 g, 81%) as a white foam: R_f = 0.56 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −64 (*c* 1.4, $CDCl_3$); $C_{42}H_{52}FN_3O_7SSi$; MW = 790.0271 g/mol; IR (neat) ν_{max} 2963, 2850, 1722, 1661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.43 (d, *J* = 7.0 Hz, 1H), 8.07−8.02 (m, 4H), 7.89 (d, *J* = 6.4 Hz, 2H), 7.65−7.42 (m, 10H), 6.32 (appd, *J* = 32.1 Hz, 1H), 5.14 (dd, *J* = 46.7, 0.8 Hz, 1H), 4.73 (d, *J* = 10.6 Hz, 1H), 4.68 (dd, *J* = 12.1, 2.1 Hz, 1H), 4.51 (d, *J* = 10.6 Hz, 1H), 4.43 (dd, *J* = 6.3, 2.4 Hz, 1H), 4.29 (ddd, *J* = 12.0, 6.4, 2.7 Hz, 1H), 1.44 (d, *J* = 1.0 Hz, 3H), 1.33 (s, 9H), 0.87 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 166.31, 166.29, 162.3, 155.0, 148.0, 133.4, 133.3, 133.2, 130.2, 130.0, 129.76, 129.74, 129.3, 128.651, 128.649, 128.57, 127.6, 96.5, 96.2 (d, *J* = 185.1 Hz), 73.8, 67.9 (d, *J* = 7.6 Hz), 65.0 (d, *J* = 7.8 Hz), 60.5 (d, *J* = 19.8 Hz), 46.5 (d, *J* = 18.6 Hz), 45.8, 31.2, 26.0, 18.4, 16.7 (d, *J* = 7.6 Hz), −3.8, −4.8 ppm; HRMS calcd for $C_{42}H_{52}FN_3O_7SSiNa$ [M + Na^+] 812.3171, found 812.3189 (2.21 ppm).

*(−)-(2R,3S)-2-((1R,2S)-2-(4-Benzamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**S25**).* To a solution of **51** (0.41 g, 0.52 mmol, 1.0 equiv) in anhydrous THF (5.0 mL, 0.10 M) in a plastic vial at 0 °C was added HF-pyridine (2.0 mL, 4 mL/mmol, ∼70% HF). The reaction was stirred for 79 h at 25 °C. A saturated solution (3.0 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **S25** (0.26 g, 74%): R_f = 0.34 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −44 (*c* 1.1, $CDCl_3$); $C_{36}H_{38}FN_3O_7S$; MW = 675.7662 g/mol; IR (neat) ν_{max} 3306, 3066, 2963, 1712, 1648 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.51 (d, *J* = 6.2 Hz, 1H), 8.09−8.00 (m, 4H), 7.89 (s, 2H), 7.72−7.39 (m, 10H), 6.58 (appd, *J* = 31.8 Hz, 1H), 4.96 (appd, *J* = 46.1 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.74 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.53−4.46 (m, 1H), 4.32 (apps, 1H), 3.92 (s, 1H), 1.37 (s, 3H), 1.31 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.7, 166.2, 162.5, 155.8, 147.7, 133.5, 133.4, 133.3, 130.0, 129.96, 129.89, 129.86, 129.3, 128.7, 128.520, 128.518, 127.7, 99.3 (d, *J* = 185.4 Hz), 97.3, 72.9 (d, *J* = 3.3 Hz), 66.3 (d, *J* = 3.7 Hz), 65.7 (d, *J* = 3.5 Hz), 60.9 (d, *J* = 19.9 Hz), 45.8 (d, *J* = 17.4 Hz), 45.7, 31.1, 16.0 (d, *J* = 6.2 Hz) ppm; HRMS calcd for $C_{36}H_{38}FN_3O_7SNa$ [M + Na^+] 698.2307, found 698.2324 (2.43 ppm).

*(+)-((2S,3R,4R,5R)-5-(4-Benzamido-2-oxopyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrofuran-2,3-diyl)bis(methylene) Dibenzoate (**S26**).* To a solution of **S25** (0.104 g, 0.15 mmol, 1.0 equiv) in anhydrous DCM (1.6 mL, 0.10 M) at 0 °C was added NIS (0.104 g, 0.46 mmol, 3.0 equiv). The reaction was stirred for 16 h at 25 °C. A saturated solution (1.0 mL) of $Na_2S_2O_3{\cdot}5H_2O$ was added, and the aqueous layer was extracted with DCM (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **S26** (43 mg, 48%): R_f = 0.20 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ +90 (*c* 1.0, $CDCl_3$); $C_{32}H_{28}FN_3O_7$; MW = 585.5790 g/mol; IR (neat) ν_{max} 3301, 1723, 1675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.24 (d, *J* = 7.3 Hz, 1H), 8.10−8.01 (m, 4H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.71−7.42 (m, 10H), 5.97 (appd, *J* = 19.8 Hz, 1H), 5.20 (appd, *J* = 49.6 Hz, 1H), 4.80 (dd, *J* = 11.8, 7.4 Hz, 1H), 4.74 (dd, *J* = 7.4, 3.3 Hz, 1H), 4.63 (dd, *J* = 11.8, 3.3 Hz, 1H), 4.57 (d, *J* = 11.2 Hz, 1H), 4.52 (dd, *J* = 11.2, 2.7 Hz, 1H), 1.11 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 166.2, 166.1, 162.9, 155.1, 143.7, 133.7, 133.6, 133.5, 132.9, 129.9, 129.8, 129.5, 129.4, 129.3, 128.78, 128.75, 127.66, 100.4 (d, *J* = 191.8 Hz), 96.9, 92.1 (d, *J* = 39.3 Hz), 83.2, 65.4 (d, *J* = 11.8 Hz), 63.2, 47.1 (d, *J* = 16.7 Hz), 15.4 (d, *J* = 5.5 Hz) ppm; HRMS calcd for $C_{32}H_{28}FN_3O_7Na$ [M + Na^+] 608.1803, found 608.1814 (1.66 ppm).

*(+)-4-Amino-1-((2R,3R,4R,5S)-3-fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrofuran-2-yl)pyrimidin-2(1H)-one (**52**).* To a solution of **S26** (83 mg, 0.14 mmol, 1.0 equiv) in MeOH (1.3 mL, 0.13 M) at 0 °C was added NaOMe (0.14 mL, 0.57 mmol, 4.0 equiv, 25 wt % solution in MeOH). The reaction was stirred for 16 h at 25 °C. Formic acid (∼2 drops) was added to neutralize the reaction mixture before concentration. Purification by reverse phase C18 (H_2O/MeOH, 90:10) provided **52** (20 mg, 52%): $[\alpha]_D^{25}$ +58 (*c* 1.2, CD_3OD); $C_{11}H_{16}FN_3O_4$; MW = 273.2608 g/mol; IR (neat) ν_{max} 3445, 2528,1651 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.98 (d, *J* = 7.5 Hz, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 5.90 (dd, *J* = 18.9, 2.3 Hz, 1H), 4.90 (dd, *J* = 51.7, 2.3 Hz, 1H), 4.19 (appt, *J* = 5.0 Hz, 1H), 3.83−3.75 (m, 2H), 3.70 (d, *J* = 10.9 Hz, 1H), 3.64 (dd, *J* = 11.1, 2.3 Hz, 1H), 1.01 (s, 3H) ppm *OH and* NH_2 *signals missing possibly due to exchange in* CD_3OD; ^{13}C NMR (125 MHz, CD_3OD) δ 167.8, 158.3, 142.0, 102.6 (d, *J* = 188.4 Hz), 96.1, 91.5 (d, *J* = 37.5 Hz), 86.5, 64.6 (d, *J* = 12.2 Hz), 62.2, 49.9, 15.2 (d, *J* = 4.5 Hz) ppm; HRMS calcd for $C_{11}H_{16}FN_3O_4Na$ [M + Na^+] 296.1017, found 296.1006 (−3.69 ppm).

*(−)-(2R,3S)-2-((1R,2S)-2-(tert-Butylthio)-2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-1-fluoroethyl)-2-methyl-3-((methylsulfonyl)oxy)butane-1,4-diyl Dibenzoate (**S27**).* To a solution of **S23** (0.18 g, 0.31 mmol, 1.0 equiv) in anhydrous DCM (1.0 mL, 0.30 M) at 0 °C were added triethylamine (20 μL, 1.24 mmol, 4.0 equiv) and methanesulfonyl chloride (80 μL, 0.96 mmol, 3.1 equiv). The reaction was stirred for 16 h at 25 °C. A 1.0 N solution (0.50 mL) of HCl was added, and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (DCM/acetone, 90:10) provided **S27** (100 mg, 49%): R_f = 0.53 (DCM/acetone, 90:10); $[\alpha]_D^{25}$ −27 (*c* 1.3, $CDCl_3$); $C_{30}H_{35}FN_2O_9S_2$; MW = 650.7353 g/mol; IR (neat) ν_{max} 3221, 2966, 1690 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1H), 8.13−8.02 (m, 4H), 7.90 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.61−7.56 (m, 2H), 7.49−7.45 (m, 4H), 6.24 (appd, *J* = 31.9 Hz, 1H), 5.80 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.69 (d, *J* = 7.7 Hz,

DOI: 10.1021/acs.joc.6b01845
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1H), 5.01−4.86 (m, 2H), 4.68 (d, J = 11.3 Hz, 1H), 4.55 (dd, J = 12.3, 9.1 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 3.08 (s, 3H), 1.49 (d, J = 1.4 Hz, 3H), 1.36 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.17, 166.15, 162.6, 150.3, 142.0 (d, J = 2.7 Hz), 133.7, 133.6, 129.91, 129.89, 129.5, 129.4, 128.8, 128.7, 103.0, 98.4 (d, J = 187.5 Hz), 82.2, 64.4 (d, J = 8.0 Hz), 64.3 (d, J = 5.3 Hz), 58.6 (d, J = 19.8 Hz), 46.0, 45.5 (d, J = 18.0 Hz), 39.5, 31.1, 17.9 (d, J = 6.5 Hz) ppm; HRMS calcd for $C_{30}H_{35}FN_2O_9S_2Na$ [M + Na^+] 673.1660, found 673.1674 (2.0 ppm).

*(−)-((2R,3S,4R,5S)-5-(2,4-Dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) Dibenzoate (**S28**).* A solution of **S27** (89 mg, 0.14 mmol, 1.0 equiv) in 2,6-lutidine (3.0 mL, 0.05 M) was refluxed for 5 h at 160 °C. A 1.0 N solution (2.0 mL) of HCl was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 30:70) provided **S28** (62 mg, 91%): R_f = 0.50 (hexanes/EtOAc, 30:70); $[\alpha]_D^{25}$ −94 (c 0.8, $CDCl_3$); $C_{25}H_{23}FN_2O_6S$; MW = 498.5233 g/mol; IR (neat) ν_{max} 3199, 3065, 1691 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.06−7.98 (m, 5H), 7.62−7.53 (m, 2H), 7.48−7.42 (m, 4H), 6.60 (dd, J = 25.2, 3.8 Hz, 1H), 5.80 (dd, J = 8.3, 2.3 Hz, 1H), 5.04 (dd, J = 52.5, 3.8 Hz, 1H), 4.82−4.76 (m, 1H), 4.73−4.66 (m, 2H), 4.53 (dd, J = 11.2, 2.0 Hz, 1H), 3.78−3.71 (m, 1H), 1.48 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 166.0, 162.4, 150.9, 143.0 (d, J = 4.8 Hz), 133.7, 133.6, 129.9, 129.8, 129.5, 129.4, 128.74, 128.69, 102.4, 98.6 (d, J = 191.6 Hz), 65.6 (d, J = 6.1 Hz), 64.6 (d, J = 7.4 Hz), 62.6 (d, J = 16.7 Hz), 55.4, 51.8 (d, J = 15.6 Hz), 21.3 (d, J = 7.8 Hz) ppm; HRMS calcd for $C_{25}H_{23}FN_2O_6SNa$ [M + Na^+] 521.1153, found 521.1157 (0.79 ppm).

*(−)-1-((2S,3R,4S,5R)-3-Fluoro-4,5-bis(hydroxymethyl)-4-methyltetrahydrothiophen-2-yl)pyrimidine-2,4(1H,3H)-dione (**53**).* To a solution of **S28** (54 mg, 0.11 mmol, 1.0 equiv) in MeOH (0.9 mL, 0.13 M) at 0 °C was added NaOMe (20 μL, 0.054 mmol, 0.5 equiv, 25 wt % solution in MeOH). The reaction was stirred for 16 h at 25 °C. A 1 N HCl solution (∼10 drops) was added to neutralize the reaction mixture before concentration. Purification by flash chromatography (DCM/MeOH, 95:5) provided **53** (25 mg, 80%): R_f = 0.31 (DCM/MeOH, 95:5); $[\alpha]_D^{25}$ −63 (c 0.7, CD_3OD); $C_{11}H_{15}FN_2O_4S$; MW = 290.3112 g/mol; IR (neat) ν_{max} 3333, 2883, 1701 cm^{-1}; ^{1}H NMR (500 MHz, $(CD_3)_2CO$) δ 8.03 (d, J = 6.9 Hz, 1H), 6.47 (appd, J = 25.4 Hz, 1H), 5.64 (d, J = 7.9 Hz, 1H), 4.91 (appd, J = 53.3 Hz, 1H), 4.11−4.01 (m, 1H), 3.87−3.69 (m, 3H), 3.36 (appt, J = 7.1 Hz, 1H), 1.34 (s, 3H) ppm *OH and NH signals missing possibly due to exchange in* $(CD_3)_2CO$; ^{13}C NMR (125 MHz, CD_3OD) δ 165.9, 152.7, 145.3 (d, J = 4.7 Hz), 101.8, 100.2 (d, J = 188.9 Hz), 64.5 (d, J = 5.3 Hz), 63.8 (d, J = 16.8 Hz), 62.9 (d, J = 7.6 Hz), 60.9 (d, J = 1.5 Hz), 54.5 (d, J = 15.8 Hz), 21.2 (d, J = 8.7 Hz) ppm; HRMS calcd for $C_{11}H_{15}FN_2O_4SNa$ [M + Na^+] 313.0629, found 313.0635 (1.94 ppm).

*(−)-(2R,3S)-2-((1R,2S)-2-(4-Benzamido-2-oxopyrimidin-1(2H)-yl)-2-(tert-butylthio)-1-fluoroethyl)-2-methyl-3-((methylsulfonyl)oxy)-butane-1,4-diyl Dibenzoate (**S29**).* To a solution of **S25** (0.13 g, 0.20 mmol, 1.0 equiv) in anhydrous DCM (1.0 mL, 0.30 M) at 0 °C were added triethylamine (0.10 mL, 0.78 mmol, 4.0 equiv) and methanesulfonyl chloride (0.05 mL, 0.61 mmol, 3.1 equiv). The reaction was stirred for 16 h at 25 °C. A 1.0 N solution (0.20 mL) of HCl was added, and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **S29** (28 mg, 19%): R_f = 0.11 (hexanes/EtOAc, 50:50); $[\alpha]_D^{25}$ −50 (c 0.9, $CDCl_3$); $C_{37}H_{40}FN_3O_9S_2$; MW = 753.8566 g/mol; IR (neat) ν_{max} 2973, 1723, 1658 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.44 (d, J = 7.7 Hz, 1H), 8.13−8.04 (m, 4H), 7.89 (d, J = 7.0 Hz, 2H), 7.69−7.42 (m, 10H), 6.45 (appd, J = 32.6 Hz, 1H), 5.78 (appd, J = 8.5 Hz, 1H), 4.97 (appd, J = 54.3 Hz, 1H), 4.93 (d, J = 4.3 Hz, 1H), 4.72 (d, J = 11.2 Hz, 1H), 4.59−4.51 (m, 2H), 3.09 (s, 3H), 1.56 (s, 3H), 1.35 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.24, 166.18, 166.11, 162.5, 155.2, 147.5, 133.54, 133.50, 133.49, 130.0, 129.93, 129.6, 129.5, 129.3, 128.76, 128.74, 128.69, 127.65, 97.6 (d, J = 188.1 Hz), 97.0, 82.3, 64.5 (d, J = 7.9 Hz), 64.3 (d, J = 5.3 Hz), 60.1 (d, J = 18.8 Hz), 46.3, 45.6 (d, J = 17.7 Hz), 39.5, 31.1, 18.0 (d, J = 6.8 Hz) ppm; HRMS calcd for $C_{37}H_{40}FN_3O_9S_2Na$ [M + Na^+] 776.2082, found 776.2074 (−1.07 ppm).

*(−)-((2R,3S,4R,5S)-5-(4-Benzamido-2-oxopyrimidin-1(2H)-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) Dibenzoate (**54**).* A solution of **S29** (24 mg, 0.03 mmol, 1.0 equiv) in 2,6-lutidine (1.0 mL, 0.03 M) was refluxed for 4 h at 160 °C. Upon cooling to 25 °C, the reaction was concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 30:70) provided **54** (11.1 mg, 57%): R_f = 0.16 (hexanes/EtOAc, 30:70); $[\alpha]_D^{25}$ −87 (c 0.7, $CDCl_3$); $C_{32}H_{28}FN_3O_6S$; MW = 601.6446 g/mol; IR (neat) ν_{max} 3247, 3076, 2968, 1723, 1664 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.50 (d, J = 7.2 Hz, 1H), 8.08−7.98 (m, 4H), 7.92−7.40 (m, 12H), 6.81 (dd, J = 24.5, 3.6 Hz, 1H), 5.20 (dd, J = 52.4, 3.7 Hz, 1H), 4.87−4.81 (m, 1H), 4.73−4.67 (m, 2H), 4.59−4.53 (m, 1H), 3.80−3.75 (m, 1H), 1.51 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 166.1, 166.0 162.6, 148.4, 133.57, 133.54, 133.4, 132.1, 130.0, 129.83, 129.75, 129.6, 129.3, 128.8, 128.74 128.70, 127.7, 127.5, 98.0 (d, J = 190.8 Hz), 65.8, 64.8 (d, J = 7.1 Hz), 64.5 (d, J = 16.6 Hz), 55.8, 52.3 (d, J = 15.6 Hz), 21.4 (d, J = 8.0 Hz) ppm; HRMS calcd for $C_{32}H_{28}FN_3O_6SNa$ [M + Na^+] 624.1575, found 624.1584 (1.46 ppm).

*(−)-(2R,3S)-3-((tert-Butyldimethylsilyl)oxy)-2-((1R,2S)-2-(tert-butylthio)-2-(6-chloro-9H-purin-9-yl)-1-fluoroethyl)-2-methylbutane-1,4-diyl Dibenzoate (**55**).* Following general procedure A, 6-Cl-purine (0.37 g, 2.37 mmol, 3.5 equiv) and I_2 (0.34 g, 1.4 mmol, 2.0 equiv) were added to a solution of **37** (0.45 g, 0.68 mmol, 1.0 equiv) in anhydrous THF (7.0 mL, 0.10 M) and stirred at 25 °C for 16 h. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of only the 1,2-*syn* diastereomer. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **55** (0.42 g, 84%) as a white foam: R_f = 0.49 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ −71 (c 1.4, $CDCl_3$); $C_{36}H_{46}ClFN_4O_5SSi$; MW = 729.3761 g/mol; IR (neat) ν_{max} 2958, 2930, 2858, 1723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 1.9 Hz, 1H), 8.49 (s, 1H), 8.00−7.89 (m, 4H), 7.61−7.54 (m, 2H), 7.46−7.37 (m, 4H), 6.10 (dd, J = 30.6, 1.3 Hz, 1H), 5.20 (dd, J = 46.3, 1.3 Hz, 1H), 4.70 (d, J = 10.7 Hz, 1H), 4.64 (dd, J = 12.0, 3.4 Hz, 1H), 4.55 (d, J = 10.7 Hz, 1H), 4.32 (dd, J = 6.2, 3.5 Hz, 1H), 4.23 (ddd, J = 12.0, 6.3, 2.5 Hz, 1H), 1.50 (d, J = 1.3 Hz, 3H), 1.21 (s, 9H), 0.81 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 166.3, 152.2, 151.2, 150.4, 145.5 (d, J = 1.8 Hz), 133.5, 133.3, 131.7, 129.9, 129.71, 129.65, 129.55, 128.7, 128.6, 95.5 (d, J = 186.0 Hz), 73.6, 67.4 (d, J = 5.7 Hz), 65.1 (d, J = 7.8 Hz), 57.9 (d, J = 21.4 Hz), 46.3 (d, J = 19.0 Hz), 45.7, 31.0, 25.9, 18.4, 16.2 (d, J = 7.2 Hz), −3.9, −5.0 ppm; HRMS calcd for $C_{36}H_{46}ClFN_4O_5SSiNa$ [M + Na^+] 751.2523, found 751.2526 (0.47 ppm).

*(−)-(2R,3S)-2-((1R,2S)-2-(tert-Butylthio)-2-(6-chloro-9H-purin-9-yl)-1-fluoroethyl)-3-hydroxy-2-methylbutane-1,4-diyl Dibenzoate (**S30**).* To a solution of **55** (0.11 g, 0.16 mmol, 1.0 equiv) in anhydrous THF (0.6 mL, 0.26 M) in a plastic vial at 0 °C was added $3HF{\cdot}NEt_3$ (0.20 mL, 0.78 mmol, 5.0 equiv). The reaction was stirred for 120 h at 25 °C. A saturated solution (0.5 mL) of $NaHCO_3$ was added, and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **S30** (61 mg, 64%): R_f = 0.29 (hexanes/EtOAc, 70:30); $[\alpha]_D^{25}$ −47 (c 0.7, $CDCl_3$); $C_{30}H_{32}ClFN_4O_5S$; MW = 615.1153 g/mol; IR (neat) ν_{max} 3317, 2964, 1717 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, J = 1.8 Hz, 1H), 8.61 (s, 1H), 8.08−7.97 (m, 4H), 7.63−7.55 (m, 2H), 7.49−7.40 (m, 4H), 6.58 (dd, J = 31.3, 0.7 Hz, 1H), 5.09 (d, J = 11.5 Hz, 1H), 5.00 (dd, J = 45.7, 0.7 Hz, 1H), 4.65 (dd, J = 11.7, 2.3 Hz, 1H), 4.58−4.53 (m, 2H), 4.22−4.16 (m, 1H), 3.51 (d, J = 3.7 Hz, 1H), 1.41 (d, J = 1.8 Hz, 3H), 1.21 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 166.9, 152.3, 151.4, 150.5, 145.5 (d, J = 2.1 Hz), 133.7, 133.5, 131.8, 129.9, 129.8, 129.7, 129.6, 128.7, 128.6, 98.1 (d, J = 186.3 Hz), 73.6 (d, J = 2.9 Hz), 66.2 (d, J = 3.5 Hz), 66.1 (d, J = 4.7 Hz), 58.2 (d, J = 21.1 Hz), 45.7, 45.6 (d, J = 17.8 Hz), 31.0, 17.2 (d, J = 6.0 Hz)

DOI: 10.1021/acs.joc.6b01845
J. Org. Chem. 2016, 81, 10769−10790

ppm; HRMS calcd for $C_{30}H_{32}ClFN_4O_5SNa$ [M + Na^+] 637.1658, found 637.1672 (2.1 ppm).

*((2R,3S,4R,5S)-5-(6-(Benzylamino)-9H-purin-9-yl)-4-fluoro-3-methyltetrahydrothiophene-2,3-diyl)bis(methylene) Dibenzoate (**56**).* To a solution of **S30** (46 mg, 0.08 mmol, 1.0 equiv) in anhydrous DCM (0.30 mL, 0.30 M) at 0 °C were added triethylamine (42 μL, 0.30 mmol, 4.0 equiv) and methanesulfonyl chloride (20 μL, 0.23 mmol, 3.1 equiv). The reaction was stirred for 16 h at 25 °C. H_2O (0.20 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 2 mL). The combined organic layers were washed with a saturated solution of $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 70:30) resulted in the C4−Ms thioaminal, but it was not clean and used as is for the cyclization. A solution of C4−Ms thioaminal (37 mg, 0.05 mmol, 1.0 equiv) in 2,6-lutidine (1.0 mL, 0.05 M) was refluxed for 4 h at 160 °C. Upon cooling to 25 °C, the reaction was concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided the cyclized product (11.4 mg, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.68 (s, 1H), 8.02 (dd, J = 31.4, 7.1 Hz, 4H), 7.57 (dd, J = 13.3, 7.0 Hz, 2H), 7.44 (t, J = 7.6 Hz, 4H), 6.70 (dd, J = 23.7, 2.8 Hz, 1H), 5.09 (dd, J = 52.4, 2.6 Hz, 1H), 4.91 (appt, J = 9.7 Hz, 1H), 4.85−4.75 (m, 2H), 4.62 (d, J = 11.1 Hz, 1H), 3.86 (appt, J = 7.3 Hz, 1H), 1.57 (s, 3H) ppm; HRMS calcd $C_{26}H_{22}ClFN_4O_4SNa$ [M + Na^+] 563.0927, found 563.0934 (1.30 ppm). Full characterization was not done as the product still contained some 2,6-lutidine. To a solution of the cyclized product (11 mg, 0.02 mmol, 1.0 equiv) in isopropyl alcohol (0.20 mL, 0.10 M) were added benzylamine (3 μL, 0.03 mmol, 1.3 equiv) and DIPEA (10 μL, 0.06 mmol, 3.0 equiv). The reaction mixture was refluxed for 16 h at 70 °C. A saturated solution of NH_4Cl (0.1 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 1 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **56** (8.8 mg, 69%): R_f = 0.17 (hexanes/EtOAc, 50:50); $C_{33}H_{30}FN_5O_4S$; MW = 611.6858 g/mol; IR (neat) ν_{max} 3263, 3065, 2941, 1717, 1620 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.29 (d, J = 3.3 Hz, 1H), 8.02 (ddd, J = 32.0, 5.0, 3.2 Hz, 4H), 7.59−7.54 (m, 2H), 7.48−7.27 (m, 9H), 6.64 (dd, J = 24.7, 3.6 Hz, 1H), 6.10 (s, 1H), 5.06 (dd, J = 52.0, 3.6 Hz, 1H), 4.91−4.79 (m, 4H), 4.77 (d, J = 11.3 Hz, 1H), 4.60 (dd, J = 11.3, 1.4 Hz, 1H), 3.80 (appt, J = 7.6 Hz, 1H), 1.55 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.14, 166.08, 155.0, 153.4, 141.03, 140.99, 138.5, 133.6, 133.5, 129.9, 129.8, 129.7, 129.6, 128.9, 128.70, 128.67, 127.9, 127.7, 119.7, 98.1 (d, J = 192.0 Hz), 66.1 (d, J = 6.1 Hz), 64.9 (d, J = 6.9 Hz), 60.3 (d, J = 18.0 Hz), 55.1, 52.0 (d, J = 15.7 Hz), 44.9, 21.6 (d, J = 7.7 Hz) ppm; HRMS calcd for $C_{33}H_{31}FN_5O_4S$ [M + H^+] 612.2075, found 612.2073 (−0.40 ppm).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01845.

X-ray crystallographic data for compound **35** (CIF)

^{1}H NMR and ^{13}C NMR spectra for all new compounds along with details concerning the computational method, energies, and Cartesian coordinates for all of the transition structures and intermediate geometries (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was enabled in part by WestGrid (www.westgrid.ca) and Compute Canada−Calcul Canada (www.computecanada.ca). Funding for this research has been granted from Natural Sciences and Engineering Research Council (NSERC), Fonds Québécois de la Recherche sur la Nature et les Technologies (FQRNT) and the Terry Fox Research Institute. NSERC and FQRNT scholarships as well as support from the Collaborative Research and Training Experience grant from NSERC (ChemNet, SGC, Toronto) to S.D. are gratefully acknowledged. SGC is a registered charity that receives funds from AbbVie, Bayer Pharma AG, Boehringer Ingelheim, Canada Foundation for Innovation, Eshelman Institute for Innovation, Genome Canada, Innovative Medicines Initiative (EU/EFPIA), Janssen, Merck & Co., Novartis Pharma AG, Ontario Ministry of Economic Development and Innovation, Pfizer, SaoPaulo Research Foundation-FAPESP, Takeda, and the Wellcome Trust.

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J. Org. Chem. 2016, 81, 10769−10790