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Investigation of Diastereoselective Acyclic α-Alkoxydithioacetal Substitutions Involving Thiacarbenium Intermediates

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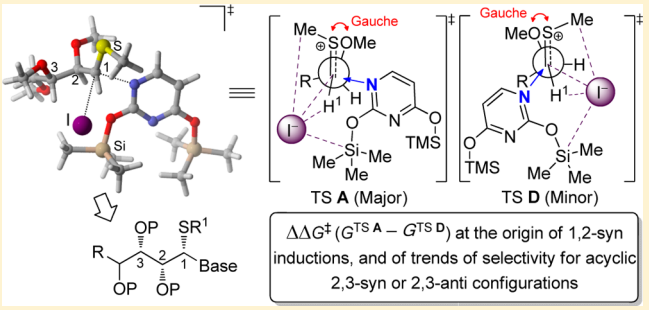
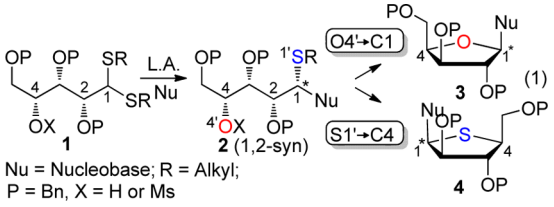
Supporting Information

ABSTRACT: Reported herein is an experimental and theoretical study that elucidates why silylated nucleobase additions to acyclic α-alkoxythiacarbenium intermediates proceed with high 1,2-syn stereocontrol (anti-Felkin−Anh), which is opposite to what would be expected with corresponding activated aldehydes. The acyclic thioaminals formed undergo intramolecular cyclizations to provide nucleoside analogues with anticancer and antiviral properties. The factors influencing the selectivity of the substitution reaction have been examined thoroughly. Halothioether species initially form, ionize in the presence (low dielectric media) or absence (higher dielectric media) of the nucleophile, and react through S_N2-like transition structures (TS **A** and **D**), where the α-alkoxy group is gauche to the thioether moiety. An important, and perhaps counterintuitive, observation in this work was that calculations done in the gas phase or low dielectric media (toluene) are essential to locate the product- and rate-determining transition structures (C−N bond formation) that allow the most reasonable prediction of selectivity and isotope effects for more polar solvents (THF, MeCN). The $\Delta\Delta G^{\ddagger}$ ($G^{TSA-TSD}$) obtained *in silico* are consistent with the preferential formation of 1,2-syn product and with the trends of stereocontrol displayed by 2,3-anti and 2,3-syn α,β-bis-alkoxydithioacetals.



INTRODUCTION

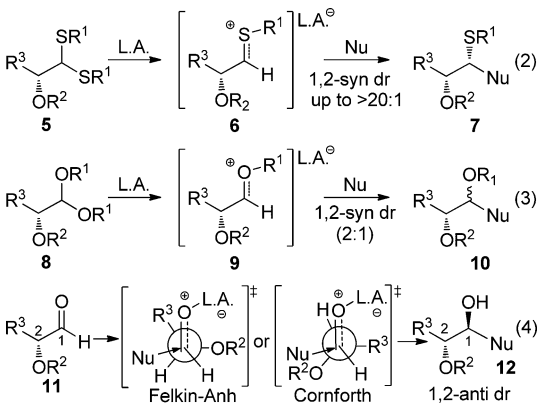
Stereocontrolled N-glycosylation reactions remain an ongoing challenge and are crucial for the efficient synthesis of nucleoside analogues, arguably the most important class of anticancer and antiviral agents.[1,2] In the course of the development of acyclic approaches for the synthesis of nucleoside analogues (eq 1), we



(1)

observed that silylated nucleobases add to α-alkoxydithioacetals (**1**) with high 1,2-syn selectivity (anti-Felkin−Anh).[3,4] The acyclic thioaminals (**2**) can undergo two distinct and versatile stereoselective S_N2-like intramolecular cyclizations. A first mode of cyclization leads to D-1,2-trans nucleoside analogues **3** through displacement of the activated thioether group with complete inversion of the C1 stereocenter. In the second mode, it is the C4 stereocenter that is inverted, while the stereochemistry of the thioaminal center is maintained to yield L-1,2-cis-4-thionucleosides **4**.

The high 1,2-syn inductions observed for nucleobase coupling to dithioacetal (**5**) are intriguing, given that corresponding acetals (**8**) lead to marginal selectivities (eqs 2 and 3).[5]



Moreover, acyclic acetals are generally anticipated to react through free or contact carbenium ion intermediates (thiacarbenium[6] **6** and oxocarbenium[7−9] **9**) and should therefore provide selectivities

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comparable to those observed with corresponding activated aldehydes. Chiral carbenium precursors not bearing an α-electron withdrawing group follow that trend and furnish the Felkin[10] product.[6,11] α-Alkoxyaldehydes **11**, however, are 1,2-anti selective in the absence of chelate formation (eq 4, Felkin–Anh[10,12] or Cornforth[13,14]), giving opposite inductions to the ones observed from **5** or **8**.

In order to understand trends of selectivity for α-alkoxyacetals, mechanistic insights are essential. The mechanism of a given substitution reaction is, however, challenging to decipher because they often proceed through borderline S_N1–S_N2 mechanisms, which have been at the center of a great deal of controversy.[7,15−18] Representation of their potential energy diagrams is helpful to differentiate these proposed reaction types (Figure 1).[19,20]

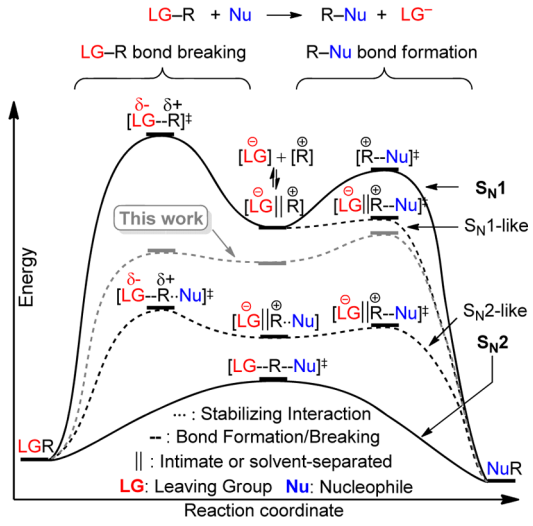


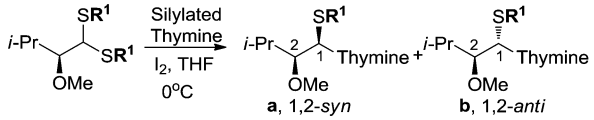
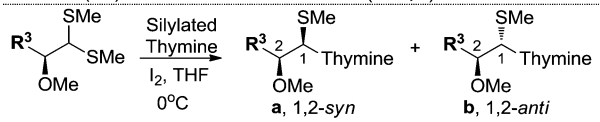
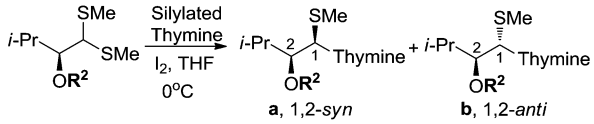
Figure 1. Potential energy diagrams for representative S_N1, S_N1-like, S_N2, and S_N2-like mechanisms in a solvent.[19,20] The work presented herein aimed at determining the preferred reaction pathway for nucleobase additions to halothioethers.

A substitution qualifies as an S_N1 scenario if formation of the free carbenium species (thia-**6** or oxo-**9**) is rate-determining (S_N1, Figure 1). The subsequent nucleophile (Nu) addition would then represent the product-determining step. In an S_N1-like mechanism, the nucleophile attack occurs on ion pairs (intimate or solvent-separated) formed after cleavage of the LG–R covalent bond. When the slow step (ion pair or product formation) involves the nucleophile, the substitution reaction functions more as an S_N2 mechanism.[21,22] S_N2 reactions involving an intermediate ion pair are termed S_N2-like,[23] since they do not meet the concerted bond-forming/bond-breaking criteria of classical S_N2 reactions (Figure 1).[24] The counterion and nucleophile can be more (associative S_N2-TS) or less ("exploded" TS) bound at the reacting carbon.[23] Under conditions allowing fast ion pair equilibration, S_N1-like and S_N2-like mechanisms can give rise to a Curtin–Hammett scenario,[25,26] where it is the rate of R–Nu bond formation that dictates the stereochemical outcome of the substitution reaction. The present study aimed at elucidating the nature of both the ionization and nucleobase addition steps, in order to better understand the mechanism and selectivity of dithioacetal substitutions.

RESULTS AND DISCUSSION

A substrate model study was undertaken to identify contributing factors to the 1,2-syn induction for the substitution of

Table 1. Substitution of Dithioacetals with Various R^1, R^2, and R^3 Groups[a]

Entry	R^1, R^2 or R^3	Ratio (**a**:**b**)[b]	Yield (%)[c]
			
1	(**14**) Me	11:1	(**15a,b**) 85
2	(**16**) i-Pr	9:1	(**17a,b**) 82
3	(**18**) t-Bu	9:1	(**19a,b**) 92
			
4	(**20**) Ph	3:1	(**21a,b**) 90
5	(**22**) $-CH_2Ph$	2:1	(**23a,b**) 83
1[*]	(**14**) i-Pr	11:1	(**15a,b**) 85
6	(**24**) t-Bu	>20:1	(**25a,b**) 81
			
7	(**26**)[d] TBS	12:1	(**27a,b**) 86

[a]Silylated thymine (2.0 equiv), I_2 (2.0 equiv), THF (0.1 M), 0 °C, 16 h. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. [c]Isolated yields. [d]$Hg(OAc)_2$ and TMSOTf activation in DCM. [*]Entry 1 represented differently.

dithioacetals by silylated nucleobase (Table 1). Dimethyl-, diisopropyl-, and ditertbutyl-dithioacetals gave comparable high 1,2-syn selectivity (entries 1–3, Table 1). With a secondary chain or a phenyl group attached at C2, the selectivity dropped significantly (entries 4 and 5). On the other hand, *i*Pr or *t*Bu side chains gave higher 1,2-syn selectivity (entries 1 and 6, Table 1). Methoxy or silyloxy C2 groups provided high 1,2-syn inductions (entries 1 and 7, Table 1), comparable to what has typically been observed on different substrates bearing a benzyloxy group at C2.[3] Dithioacetal **14** was selected to explore the different plausible mechanisms for this reaction, experimentally and *in silico*.

As presented in Table 2, various activating agents were examined to perform the nucleophilic substitution reaction. Substitution of **14** at 0 °C provided comparable 1,2-syn selectivity in the presence of I_2, Br_2, or $Me_2S(SMe)BF_4$ (entries 1, 3, and 4, Table 2). Treatment of **14** with $Hg(OAc)_2$ generated acetate **28**, which was either treated *in situ* with TMSOTf and the nucleobase (entries 5 and 6, Table 2) or purified by flash chromatography before being reacted with the nucleobase using TMSI, TMSBr, or TMSOTf (entries 7–9, Table 2). These two protocols provided the 1,2-syn product with comparable diastereoselectivity, but the *in situ* method gave higher yields. The selectivity measured at different reaction temperatures suggests that the substitution reaction is under kinetic control (entries 1 and 2 and 5 and 6).

Study of the Activation of Dithioacetals. ^{1}H NMR spectroscopic studies confirmed the formation of halothioether intermediates after treating the acyclic dithioacetal **14** with Br_2 (Figure 2).[27] Upon addition of the halogen to the dithioacetal, two new species, which display characteristic chemical shifts for **29a,b**, are rapidly formed in approximately a 1:1.6 ratio. Upon addition of the silylated thymine, these species are seemingly converted to product intermediates **30a** and **30b**, which after

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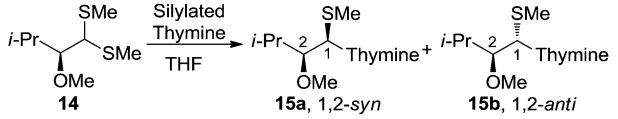
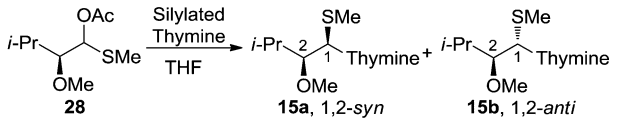
Table 2. Substitution of Dithioacetal 14 Using Various Activation Protocols[a]

Entry	Activating Agent	T(°C)	Ratio(**a**:**b**)[b]	Yield(%)[c]
				
	14	**15a**, 1,2-*syn*		**15b**, 1,2-*anti*
1	I_2	0 °C	11:1	85
2	I_2	70 °C	2 :1	81
3	Br_2	0 °C	11:1	83
4	$Me_2S(SMe)BF_4$	0 °C	14:1	79
5	$Hg(OAc)_2$, TMSOTf	0 °C	12:1	88
6	$Hg(OAc)_2$, TMSOTf	25 °C	5:1	82
				
	28	**15a**, 1,2-*syn*		**15b**, 1,2-*anti*
7	TMSI	0 °C	14:1	51
8	TMSBr	0 °C	14:1	54
9	TMSOTf	0 °C	13:1	38

[a]Silylated thymine (2.0 equiv), $I_2/Br_2/Me_2S(SMe)BF_4/Hg(OAc)_2$ (2.0 equiv), TMSI/TMSBr/TMSOTf (1.5 equiv), 0 °C, 16 h. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. [c]Isolated yields.

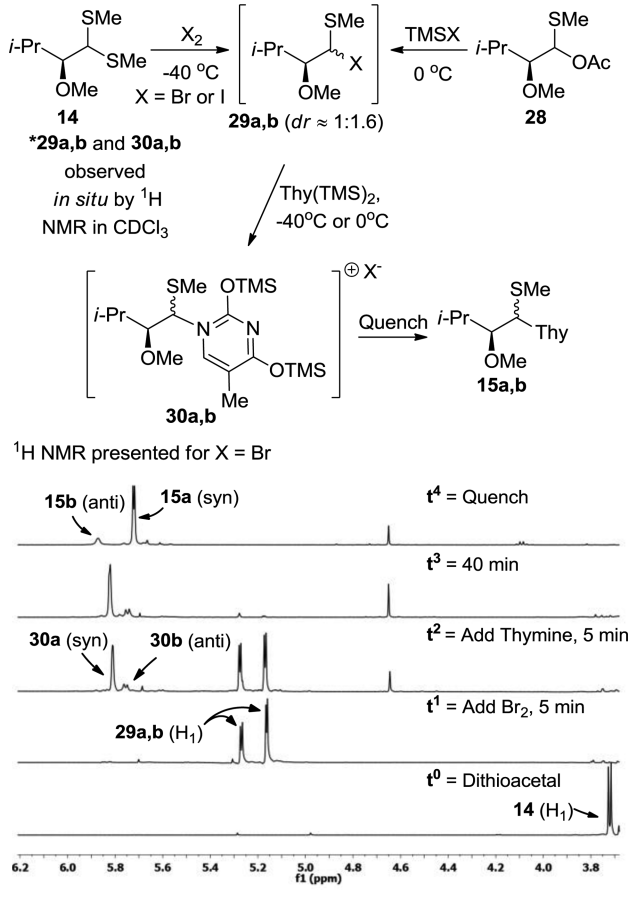
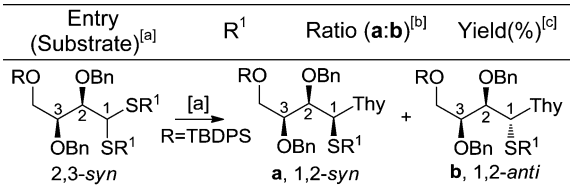
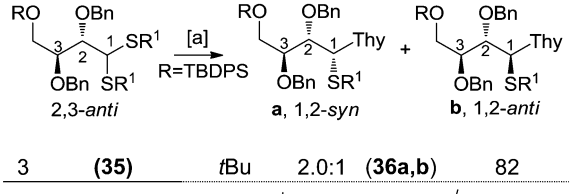
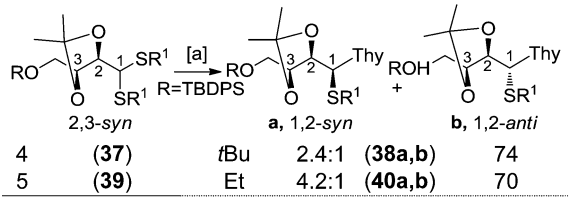
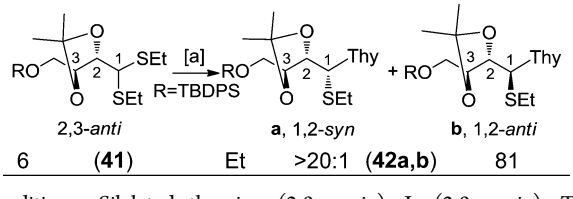


Figure 2. ^{1}H NMR spectroscopic study of the substitution of **14** or **28** by silylated thymine at −40 or 0 °C. Addition of Br_2 (1.1 equiv) to dithioacetal **14** in $CDCl_3$ showed formation of halothiointermediates **29a,b** (X = Br), which converted to **30a,b** (X = Br) upon addition of silylated thymine (3.0 equiv). After quenching with $Na_2S_2O_3$ saturated solution, thioaminals **15a,b** were observed.

hydrolysis leads to the predominant formation of 1,2-syn isomer **15a**. It is interesting to note that activation of the thioacetate **28** with TMSBr also furnished the same intermediate species **29a,b**. On the basis of these observations, the nucleobase coupling reaction does not seem to be proceeding through a classical concerted S_N2 reaction, where the product ratio would correspond to the diastereomeric mixture of halides at C1.

Substitutions of α,β-Bis-alkoxydithioacetals. To examine the impact of the 2,3-relative stereochemistry on the coupling with silylated nucleobase, different 2,3-syn and 2,3-anti bis-alkoxydithioacetals were prepared (Table 3). As previously

Table 3. Nucleobase Substitution of α,β-Bis-alkoxydithioacetals in the Presence of I_2

Entry (Substrate)[a]	R^1	Ratio (**a**:**b**)[b]	Yield(%)[c]
			
2,3-*syn*		**a**, 1,2-*syn*	**b**, 1,2-*anti*
1 (**31**)	*t*Bu	15:1 (**32a,b**)	85
2 (**33**)	Et	14:1 (**34a,b**)	84
			
2,3-*anti*		**a**, 1,2-*syn*	**b**, 1,2-*anti*
3 (**35**)	*t*Bu	2.0:1 (**36a,b**)	82
			
2,3-*syn*		**a**, 1,2-*syn*	**b**, 1,2-*anti*
4 (**37**)	*t*Bu	2.4:1 (**38a,b**)	74
5 (**39**)	Et	4.2:1 (**40a,b**)	70
			
2,3-*anti*		**a**, 1,2-*syn*	**b**, 1,2-*anti*
6 (**41**)	Et	>20:1 (**42a,b**)	81

[a]Conditions: Silylated thymine (2.0 equiv), I_2 (2.0 equiv), THF (0.1 M), 0 °C, 16 h. [b]Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. [c]Isolated yields.

observed with polyoxygenated dithioacetals,[3] 2,3-syn **31** and **33** provided high 1,2-syn dr (15:1) (entries 1 and 2, Table 3), while an erosion of selectivity (2:1) was measured with 2,3-anti **35** (entry 3, Table 3). The α,β-bis-alkoxydithioacetals are likely to adopt different conformations at the transition state level with distinct relative energies, which could influence the levels of inductions for the substitution. We therefore prepared compounds with restricted conformational freedom by linking the α- and β-alkoxy groups through formation of acetonides **37**, **39**, and **41**. To our delight, 2,3-anti acetonide **41** yielded the thioaminal products with a marked increase of selectivity (entry 6), whereas the substitution of 2,3-syn acetonides (**37**, **39**) was poorly selective (entries 4 and 5, Table 3). It is noteworthy that the size of the thioalkyl (*t*Bu vs Et) does not influence markedly the inductions observed, as previously demonstrated with model compounds **14**, **16**, and **18** (entries 1−3, Table 1).

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Overall, simple modifications of the protecting groups provides a means to reach higher 1,2-syn inductions with 2,3-anti or 2,3-syn bis-alkoxydithioacetals, increasing the scope of our approach for the synthesis of nucleoside analogues. These trends of selectivity were examined from a mechanistic standpoint *in silico*.

Previous studies aiming to rationalize trends of selectivity for additions to corresponding *α,β*-bis-alkoxyaldehydes invoked reinforcing/non-reinforcing 1,2- and 1,3-inductions.[14] Compounds **43a,b** were therefore synthesized and reacted with the silylated base in the presence of iodine in order to examine the level of induction provided by the C3-stereogenic center (Figure 3).

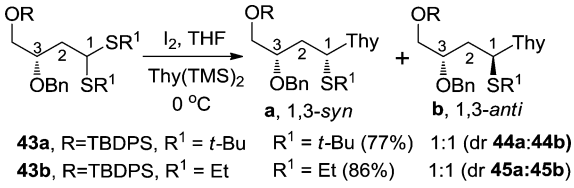

Figure 3. Substitutions of 2-deoxydithioacetals.

The formation of the thioaminal products **44** and **45** in a 1:1 ratio indicates that the *β*-alkoxy center does not provide any 1,3-stereoinduction. This suggests that the relative configuration between the C2 and C3 centers is mainly influencing the level of 1,2-syn selectivity with bis-alkoxydithioacetals, rather than individual contributions from the C2 or C3 stereogenic centers.

DFT Study of Diastereoselective Dithioacetal Substitution. The substitution mechanism of halothioether **29**, the most plausible reacting intermediate identified experimentally, was next examined by DFT calculations in Gaussian 09.[28] The Gibbs free energies reported herein were obtained for fully optimized structures at the M06-2X[29,30] level of theory using a 6-311+G** basis set in combination with LANL2DZpd[31,32] effective core potentials for bromine and iodine. The different nucleobase attack trajectories and leaving group positions were carefully probed with uracil(TMS)$_2$, which gives comparable experimental results to thymine(TMS)$_2$.[4] The mechanisms that range from S$_N$2-like to S$_N$1 were analyzed and compared *in silico*.[33] Optimizations of the transition structures and intermediates were performed in the gas phase and solvents, using the polarizable continuum solvation model (PCM).[34] These calculations indicated that the nature of the relevant transition structures, as observed in other S$_N$2 reactions,[35] is not markedly influenced by the solvent, which is also in line with measured kinetic isotope effects (see the Solvent Effects and Kinetic Isotope Effects sections, *vide infra*). The gas phase calculations can therefore provide important insights into these reactions.

An overview of the relevant intermediates and proposed transition structures for the addition of the silylated nucleobase (uracil(TMS)$_2$) to halothioether **29** is presented in Figure 4. It should be noted that uracil provides selectivities comparable to thymine and was thus used to reduce computational cost.[4] S$_N$2-like transition structures (**A** and **D**) were established to be at the rate- and product-determining steps in different solvents. For reasons described and discussed extensively in the Solvent Effects section further down, the Gibbs free energy values of TS **A** and **D** were obtained from optimized structures in toluene (PCM) that were subsequently solvated in THF. All the other intermediates presented were optimized in THF. TS **A** and **D** display relative Gibbs free energy values significantly lower than the free thiacarbenium species **46** (S$_N$1). Base coupling to the latter

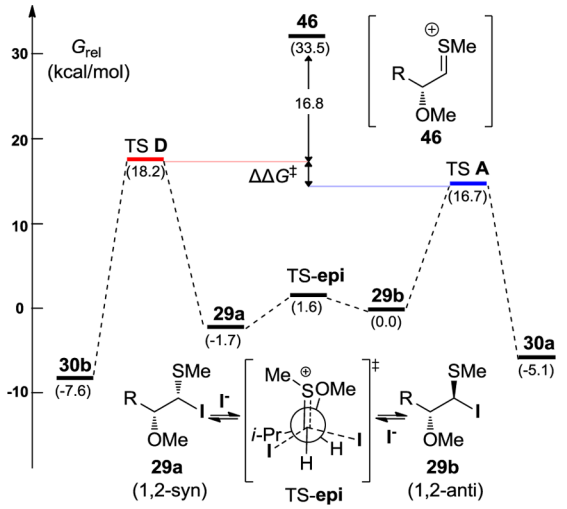

Figure 4. Relative Gibbs free energy (kcal/mol) profile in THF using the continuum solvation model (PCM) for the substitution of **29a,b** by silylated uracil through TS **D** (1,2-anti, minor) and TS **A** (1,2-syn, major). See the Supporting Information for computational details.

proceeded without encountering any energy barriers in the gas phase, THF, or MeCN (Figure 4). The relative Gibbs free energy for the epimerization (TS-**epi**) of iodothioethers **29a,b** (15.1 kcal/mol lower than TS **A**) indicates that they undergo a rapid equilibrium, as demonstrated in the ^{1}H NMR spectroscopic studies, which featured a fairly constant **29a**:**29b** ratio throughout the coupling reaction (Figure 2). The profile presented in Figure 4 is hence consistent with Curtin−Hammett kinetic control, where ΔΔ$G^‡$ between the lowest 1,2-syn (TS **A**) and 1,2-anti (TS **D**) predictive TS should correspond to the observed experimental selectivities.[25,26]

TS **A** and **D**, the lowest 1,2-syn and 1,2-anti predictive transition structures presented in Figure 5 (gas phase), were determined

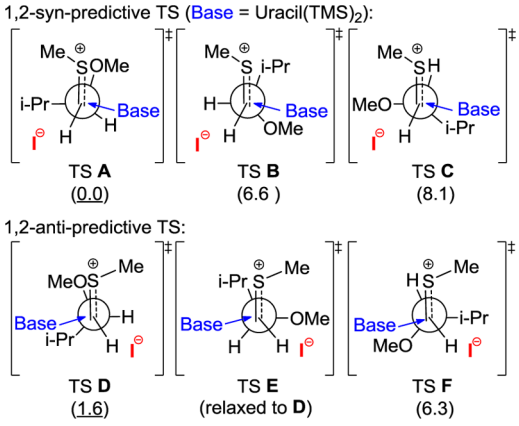

Figure 5. Lowest 1,2-syn and 1,2-anti predictive TS for the substitution of **29a,b** by silylated uracil. Gibbs free energy in the gas phase (kcal/mol). No stationary point could be found in the C2−C3 TS **E** conformation, which led to TS **D** after the transition structure optimization.

by a thorough examination of the different trajectories of base attack, counterion position, and C1−C2 conformations. In these TS, the counterion is on the opposite side of the base entrance and pyramidalization of the C1 center leads to staggered conformations. Interestingly, the lowest 1,2-syn and 1,2-anti predictive TS (**A** and **D**) both adopt a C1−C2 conformation orienting the sulfur

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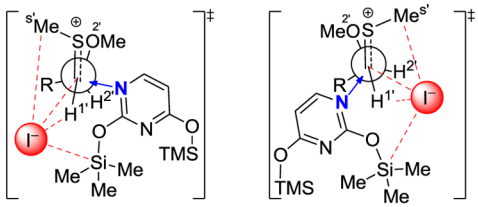
and C2-oxygen gauche to each other. The $\Delta\Delta G^{\ddagger}$ between TS **A** and **D** is in accordance with the experimentally observed preference for the 1,2-syn product.

The stabilizing interactions obtained by natural bond orbital (NBO) analyses are helpful to rationalize the preferred geometry of the transition structures (Table 4). As expected, strong

Table 4. Stabilizing Interactions (NBO Analysis) of the TS A and D in the Gas Phase[a]

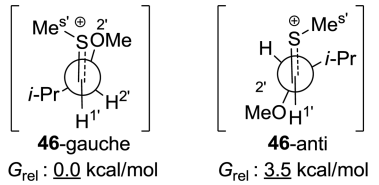


entry	stabilizing interactions	TS **A** (kcal/mol)	TS **D** (kcal/mol)
1	LP(N) → π^*(S−C1)	32.5	43.6
2	LP(I) → π^*(S−C1)	6.4	14.0
3	LP(I) → σ^*(H1′−C1)	8.5	3.8
4	LP(I) → σ^*(Me: C−H)	5.3	4.3
5	LP(I) → σ^*(TMS)	5.4	4.1
6	σ(C2−R) → π^*(S−C1)	8.6	4.1
7	σ(C2−H2′) → π^*(S−C1)	10.4	15.9
8	LP(O2′) → σ^*(S−Me$^{s'}$)	0.92	1.30

[a]LP: lone pair.

interactions are found between the π^*(S−C1) and the nitrogen sp^2 doublet of the base and, to a lesser extent, with lone pairs of the iodide (entries 1 and 2, Table 4). These interactions are stronger in TS **D**, consistent with the shorter N−C1 and I−C1 bond lengths. The free thiacarbenium (**46**-gauche and **46**-anti, Table 5) display S−C1 bond orders and bond lengths not far

Table 5. Preferred Conformations of Thiacarbenium 46 in the Gas Phase (NBO Analysis)



entry	stabilizing interaction	**46**-gauche (kcal/mol)	**46**-anti (kcal/mol)
1	σ(C2−C3$_{i\text{-}Pr}$) → π^*(S−C1)	9.0	10.4
2	σ(C2−H2′) → π^*(S−C1)	12.0	2.8
3	σ(C2−O2′) → π^*(S−C1)		2.5
4	LP(O2′) → σ^*(S−Me$^{s'}$)	1.6	
5	LP(O2′) → π^*(S−C1)		2.4

from the ones observed in TS **A** and **D**, which suggests that these TS are leaning toward contact ion pair intermediates with substantial thiacarbenium character. The bond length and interaction with the C1 center indicate a somewhat more associative mechanism for the 1,2-anti product formation (TS **D**). Significant interactions of the iodide lone pairs are additionally found with the σ^*(C−H) bonds involving the H1′, the methyl group attached to sulfur and the silicon group of the nucleobase, which all likely contribute to orienting the iodide below the thiacarbenium species (entries 3−5, Table 4). Interestingly, the R−C2 and H2′−C2 sigma bonds interact strongly with the thiacarbenium antibonding orbital. The preferred C1−C2 conformation that orients the sulfur and C2-oxygen gauche could therefore be the result of allowing a proper alignment of these sigma bonds in TS **A** and **D** (entries 6 and 7, Table 4). This orientation could also possibly favor electrostatic stabilization between the α-OMe group and the positively charged thioether group, as observed for related oxocarbenium species.[36] The calculated value from the NBO analysis, however, only suggests 0.92 and 1.30 kcal/mol stabilization for this type of interaction in TS **A** and **D** (Table 4, entry 8).

It was noted that the free thiacarbenium **46** has the same C1−C2 conformational preference as TS **A** and **D**, where the C2-oxygen and C1-sulfur are gauche (Table 5). **46**-Gauche was calculated to be 3.5 kcal/mol lower than the **46**-anti conformation (second lowest conformational minima located) in the gas phase or THF (Table 5). The stabilizing energy obtained for the sigma donation in **46**-gauche is comparable to what was found at the TS level (entries 1 and 2, Table 5). The additional stabilization energy provided by the σ(C2−O2′) bond in **46**-anti does not compensate for the sum of sigma donation calculated in **46**-gauche (entries 1−3, Table 5). Interactions between LP(O2′) provide marginal stabilization to both **46**-gauche and **46**-anti by interactions with, respectively, the σ^*(S−Me$^{s'}$) and π^*(S−C1) (entries 4 and 5, Table 5).

Nucleophilic substitution of substrates bearing C2−C3 alkoxy groups with 2,3-syn or 2,3-anti relative configurations was next examined *in silico* (Figures 6 and 7). This study required the analysis at the transition structure level of the different possible rotamers arising from the presence of additional C3−C4 alkoxy groups and possible additional interactions with the silylated base and anion. In order to reduce computational cost of these large systems, methoxy protecting groups were used *in silico*, since they display similar experimental trends of selectivity.[4]

2,3-Bis-alkoxydithioacetals Bearing C2−C3 Acetonides. As with the model substrate **14**, TS **A** and TS **D** were identified as the lowest 1,2-syn and 1,2-anti predictive transition structures for substitutions of **48** or **50** (Figure 6, R = Me). The $\Delta\Delta G^{\ddagger}$ between these TS correctly predicts higher 1,2-syn selectivity from **48** than from **50**. These computational results are in accordance with the trend of selectivity that we have observed experimentally with **37**, **39**, and **41** (Table 3). On the basis of the transition structures obtained, the higher 1,2-syn selectivity for **48** (2,3-anti) could be attributed to a destabilization of TS **D**-**48** by interactions between the C4 stereocenter and the TMS group of the base (Figure 6a), whereas the loss of 1,2-syn selectivity for the substitution of **50** (2,3-syn) could stem from an unfavorable interaction between the iodide and the C4 stereocenter in TS **A**-**50** (Figure 6b).

2,3-Bis-alkoxydithioacetals. The DFT transition structure analysis of the 2,3-syn and 2,3-antidithioacetals is in agreement with the experimental trend (Figure 7, R = Me, gas phase). The calculated $\Delta\Delta G^{\ddagger}$ (TS **A** vs **D**) predicts an unselective substitution of 2,3-anti **52** and a 1,2-syn selective coupling to 2,3-syn **54**. Unfavorable interactions between the TMS group of the base and the C3′ and C3 centers seemingly destabilize TS **A**-**52** relative to TS **D**-**52** for the substitution of **52** (Figure 7a), leading to a loss of 1,2-syn selectivity ($\Delta\Delta G^{\ddagger}$ = −0.22).

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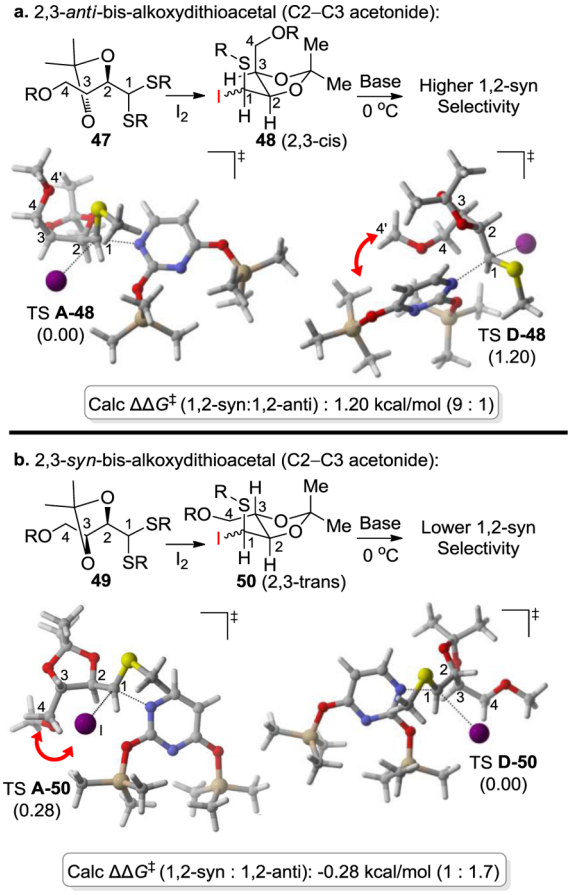

Figure 6. Lowest 1,2-syn (TS **A**) and 1,2-anti (TS **D**) transition structures for (a) 2,3-anti and (b) 2,3-syn C2,C3-acetonides (R = Me). Gas phase Gibbs free energies in kcal/mol.

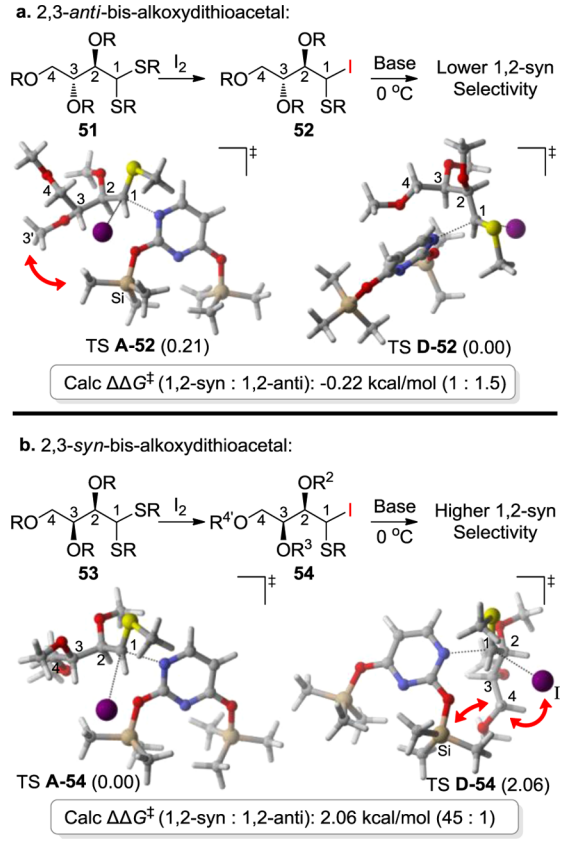

Figure 7. Lowest 1,2-syn (TS **A**) and 1,2-anti (TS **D**) transition structures for (a) 2,3-anti and (b) 2,3-syn acyclic substrates (R = Me). Gas phase Gibbs free energies in kcal/mol.

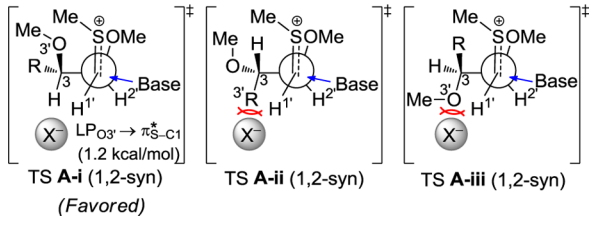

Figure 8. Important conformational preferences observed for the TS analysis of 2,3-bis-alkoxyhalothioethers.

The highly diastereoselective substitution with 2,3-syn **54** could be attributed to destabilizing interactions involving the C4 stereocenter with both the TMS group and the leaving iodide in TS **D-54** (Figure 7b).

The experimental and DFT study of 2,3-bis-alkoxydithioacetals support the proposed S_N2-like mechanism. The presence of the counterion has an important impact on the preferred conformation of the C3 stereocenter, which is oriented to avoid unfavorable steric or repulsive stereoelectronic interactions with the iodide (i.e., TS **A-i** vs TS **A-ii** or TS **A-iii**, Figure 8). A stabilizing donation between the LP(O3′) and the π^*(S−C1) (1.2 kcal/mol, Figure 8) could contribute as well to the C2−C3 conformational preference found in TS **A-54** (Figure 7b) and further increase the $\Delta\Delta G^{\ddagger}$ to allow higher 1,2-syn selectivity. A related stabilizing orbital interaction was noted for the addition to 2,3-anti acetonide **48** in TS **A-48**, but the latter was involving O4′ rather than O3′ (LP(O4′) and the π^*(S−C1), Figure 6a). NBO analysis additionally showed 1−1.4 kcal/mol stabilizing interaction involving the LP(O4′) and the π^*(N−C) of the base in TS **D-48** and TS **D-52** (Figures 6a and 7a).

Solvent Effects. The influence of solvent on the dithioacetal substitution was first probed experimentally. As seen in Table 6, a solvent with low dielectric constant (toluene) caused the 1,2 selectivity to decrease slightly (entry 2, Table 6), whereas solvents with increasing polarity (THF, MeCN, and DMSO) furnished slightly higher inductions (entries 3−5). It was also noted that the reaction times to reach completion were shorter in more polar solvents.

To examine these trends of selectivity *in silico*, the transition structures located in the gas phase were first reoptimized using the polarizable continuum (PCM) solvent model in toluene. Interestingly, after careful examination of the reaction potential surface, two TS close in energy were located in the reaction path from iodothioether **29b** to the product **30a** (1,2-syn) (Figure 9a, toluene and THF). The first transition structure, TS **G**, is characterized by the elongation of the I−C1 bond to furnish **55**, a thiacarbenium ion pair intermediate stabilized by interactions with the base. The subsequent transition structure, TS **A**, is much like the TS found in the gas phase but with slightly longer N_{base}−C1 (2.47 Å vs 2.38 Å) and I−C1 bonds (3.57 Å vs 3.49 Å). This reaction profile is characteristic of an S_N2-like mechanism (Figure 1). In THF, we could only locate TS **G**, and examination of the potential surface by intrinsic reaction path showed a weak downhill slope in the vicinity of TS **A**, which is followed by an abrupt drop in energy to the **30a**-1,2-syn structure.[37] For the formation of the 1,2-anti minor stereoisomer, the TS **D** found in toluene, THF, or MeCN displayed slightly longer N_{base}−C1 and

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Table 6. Experimental and Calculated $\Delta\Delta G^{\ddagger}$ in Different Solvents at 0 °C for the Nucleobase Substitution of Iodo and Bromothioethers 29a,b

		$\Delta\Delta G^{\ddagger}$ in kcal/mol (1,2-syn:1,2-anti)		
entry	solvent	exp[a]	calcd[c] ($G^{TSAorG} - G^{TSD}$)	
		Counterion = I		
1	vacuum		1.62	(20:1)
2	toluene[b]	1.3 (11:1)	1.25	(10:1)
3	THF[b]	1.4 (14:1)	0.18	(1.4:1)
			1.50	**(16:1)***
4	MeCN	>1.6 (>20:1)	−0.88	(1:5)
			1.67	**(22:1)***
5	DMSO	>1.6 (>20:1)	1.68	(22:1)*
		Counterion = Br		
6	vacuum		2.29	(68:1)
7	toluene[b]	0.98 (5:1)	1.89	(33:1)
8	THF[b]	1.4 (14:1)	0.53	(2.7:1)
			1.90	**(34:1)***

[a]Determined by ^{1}H NMR spectroscopic analysis of crude mixtures. [b]Ratio obtained from activation of thioacetate **28** with TMSI or TMSBr. [c]Calcd $\Delta\Delta G^{\ddagger}$ with fully optimized structures in the specified solvent (major: TS **A** for entries 1, 2, 6, and 7 or TS **G** for entries 3, 4, and 8; minor: TS **D**). *Calcd $\Delta\Delta G^{\ddagger}$ using single point solvent corrections in the specified solvent with the geometry and thermochemical corrections obtained in toluene (major, TS **A**; minor, TS **D**).

I−C1 bonds but was otherwise comparable to the one located in the gas phase (Figure 9b, toluene and THF).

The calculated $\Delta\Delta G^{\ddagger}$ between TS **A** (highest TS between **29b** and **30a**-1,2-syn) and TS **D** are in accordamce with the experimental value when the reaction was performed in toluene (1.3 vs 1.25, entry 2, Table 6). In THF or MeCN, however, the $\Delta\Delta G^{\ddagger}$ between TS **G** and TS **D** predicts a loss of 1,2-syn selectivity, in clear contrast with the measured experimental selectivity (entries 3 and 4, Table 6).[38] The calculated $\Delta\Delta G^{\ddagger}$ with a bromide counterion are found to be within the same range of energy as with the iodide in the gas phase and THF (entries 1 vs 6 and 3 vs 8, Table 6).

An important observation was that the calculated $\Delta\Delta G^{\ddagger}$ using the estimated TS **A**, rather than TS **G** in THF or MeCN, are in agreement with the experimental values (Table 6, values with an asterisk). This led us to examine the possibility that the ionization would not occur through TS **G**. In accordance with this hypothesis, we were able to locate the ionization transition structure **H** that leads to ion pair **56** (Figures 10 and 11). In electronic energy, TS **H** is 10.7 kcal/mol higher than TS **G**, because the ionized intermediate in the latter benefits from stabilizing interactions with the nucleophile (Figure 1, S_N1-like vs S_N2-like). In Gibbs free energy, however, TS **H** is lower by 3.7 kcal/mol (17.4 vs 13.6 kcal/mol, Figures 10 and 11). The most important difference between the calculated relative electronic and Gibbs free energies for TS **H** or **G** stems from the entropy correction values.[33]

The preferred pathway in Gibbs free energy (blue) would hence involve TS **H** rather than TS **G** (Figure 11, THF). TS **H** leads to thiacarbenium ion pair intermediate **56**, which could then react with the nucleobase through TS **A**. We are hence proposing that TS **A** and **D** are both at the rate-determining and product-determining steps, and should therefore be considered for the predicted selectivities in all the solvents studied.

Kinetic Isotope Effects (KIEs). In order to gain more mechanistic insights, the secondary KIEs were determined for the

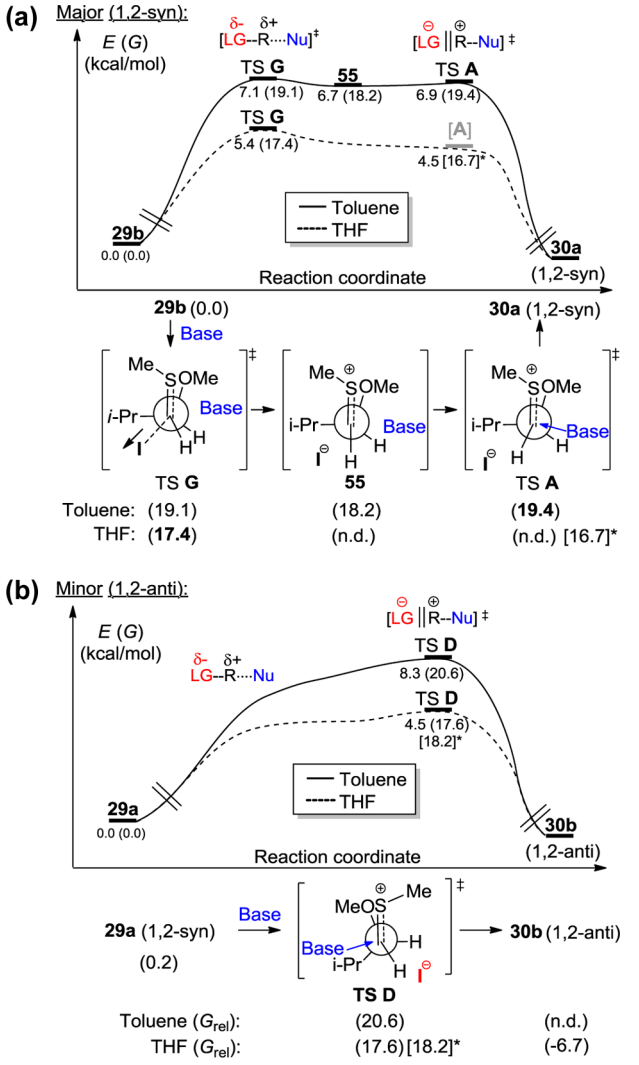

Figure 9. (a) Reaction pathway leading to major (1,2-syn) product presented with electronic and Gibbs free energy (kcal/mol) values in toluene and THF. In toluene, TS **G** (R−LG bond-breaking), **55**, and TS **A** (R−Nu bond-forming) were identified as stationary points on the potential surface, whereas only TS **G** could be located in THF. The latter can collapse to product without encountering any barriers. The electronic energy and Gibbs free energy shown for [**A**] in THF were obtained from the solvated structure identified in toluene (see also Table 6). (b) Reaction pathway leading to minor (1,2-anti) thioaminal in toluene or THF presented with electronic and Gibbs free energy (kcal/mol) values. In both solvents, TS **D** was higher in energy than intermediates in the ionization region of the reaction coordinates (see also Table 6).

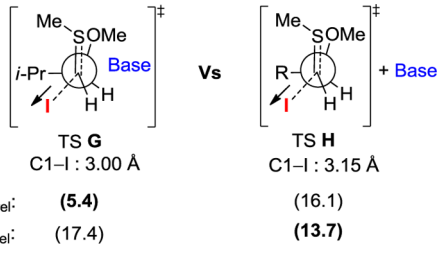

Figure 10. Ionization transition structures (R−I bond-breaking) in the presence (TS **G**) or absence (TS **H**) of the base in THF. TS **G** is lower in relative electronic energy (kcal/mol) but significantly higher than TS **H** in Gibbs free energy (kcal/mol).

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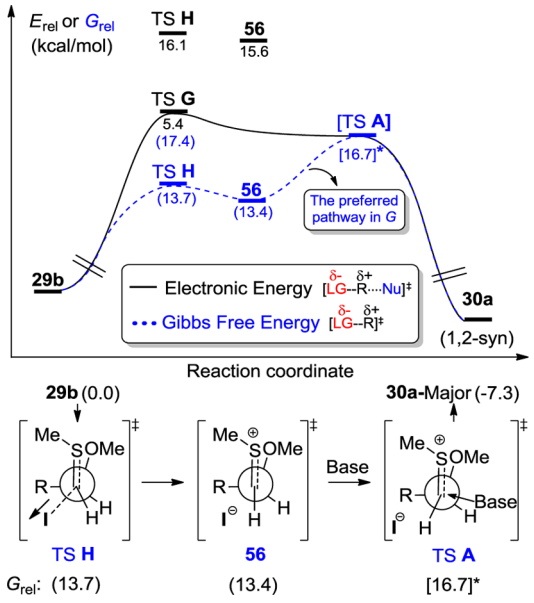

Figure 11. Diagram illustrating the reaction pathway involving halothioether **29** that leads to major (1,2-syn) thioaminal in THF (PCM). In electronic energy, TS **G** (LG−R bond-breaking in the presence of the base) is involved at the rate-determining step. In relative Gibbs free energy (kcal/mol), however, the reaction preferably proceeds through TS **H** (LG−R bond-breaking in the absence of the base) and TS **A** (R−Nu bond-forming step) is therefore clearly at the rate-limiting and product-determining step (see also Figure 9a).

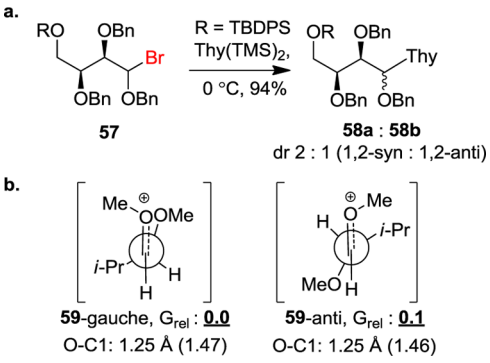

Figure 12. (a) Substitution of α-alkoxy bromoether by silylated thymine with low 1,2-syn selectivity. (b) Acyclic oxocarbenium **59** does not display a gauche conformational preference in THF, contrarily to thiacarbenium **46** (see Table 5).

substitution of 50% ^{2}H enriched bromothioether intermediate **29** (Table 7). Complete conversion of **14** or **28** to **29** after the addition of Br_2 or TMSBr could be ensured by ^{1}H NMR spectroscopic analysis of the reaction mixtures. The silylated thymine nucleobase was then added and the reactions were quenched when 20−40% conversion was reached, as determined by ^{1}H NMR and confirmed after isolation and purification of the crude mixtures. The calculated values by DFT were determined according to the transition state theory.[35] The thermochemical corrections, which provide the Gibbs free energies and are at the origin of the isotope effect, could only be determined in the gas phase and toluene for the 1,2-syn product.

The secondary α-deuterium kinetic isotope effects measured are suggesting, as observed *in silico*, that the nature of the S_N2-like transition state is not markedly influenced by the solvent polarity (Table 7, entries 1−5). Different factors have been shown to have an impact on KIEs;[39,40] the comparison of isotope effects between different reactions should hence be done with caution. Nonetheless, large positive values ($k_H/k_D \approx 1.20$) suggest a more dissociative TS with pronounced oxocarbenium character, whereas small values ($k_H/k_D \approx 1.0$) are typically obtained for more associative S_N2 TS.[21,39,41] The calculated vacuum and toluene α-deuterium effects for the 1,2-syn (1.28 and 1.24) and 1,2-anti (1.16 and 1.14) products (entries 1 and 2, Table 7) are consistent with these observations, as TS **D** was observed to display shorter bonds with the leaving halide than TS **A** (Table 4). The experimental values could be considered within the range of the 1,2-syn product calculations but are lower than expected for the 1,2-anti products. It is noteworthy that the experimental KIE values for the 1,2-syn product correspond to those reported for O-glycosylations proposed to occur through exploded-S_N2 or CIP mechanisms with pronounced oxocarbenium character at the transition state.[21,41] The more ionized nature of the S_N2-like TS **A** relative to TS **D** could also be at the origin of the higher 1,2-syn trend of selectivity in solvents of increasing dielectric constant (Table 6). TS **A** is more stabilized in polar media relative to TS **D**, which results in an increased $\Delta\Delta G^{\ddagger}$.

***α*-Alkoxyacetals versus *α*-Alkoxydithioacetals.** It appears from the present study that the high 1,2-syn selectivity observed for α-alkoxydithioacetals could largely be attributed to a conformational preference where the O2′ and SR are gauche. Free thiacarbenium intermediates display an analogous preference by 3.5 kcal/mol (Table 5). α-Alkoxyacetals typically undergo unselective substitution reactions with substrates and experimental conditions related to the reactions performed on 2,3-alkoxydithioacetals (Figure 12).[42] Although the transition state study of acyclic α-alkoxyacetals was outside the scope of this paper, we examined the preferred conformations of the acyclic oxocarbenium intermediates and found a markedly smaller difference in Gibbs free energy between **59**-gauche and **59**-anti conformations (0.1 kcal/mol, Figure 12, THF). If this lack of C1−C2 conformational bias is also present at the transition state level, the lower induction found with acyclic acetals could be attributed to competitive 1,2-anti predictive TS, such as **E** or **F** (Felkin−Anh or Cornforth TS, Figure 5). It should be noted that conditions favoring free oxocarbenium species also lead to a loss of selectivity, a phenomenon proposed to stem from reaction rate constants approaching the diffusion limit.[23]

CONCLUSIONS

The analysis of the *in silico* reaction pathways allowed us to elucidate the mechanism of the substitution of halothiothers by a nucleobase. In toluene, the pathway leading to the major (1,2-syn) thioaminal is characteristic of an S_N2-like mechanism, where the ionization occurs in the presence of the nucleophile. In THF and solvents of increasing dielectric constant, the Gibbs free energy profile indicated that the ionization follows an S_N1-like process not involving the nucleophile during the ion-pair formation. The subsequent base addition remains, however, both the rate-limiting and product-determining step and occurs in the presence of the leaving group. This substitution therefore functions as a stepwise S_N2 reaction and should reasonably be termed S_N2-like. The formation of the minor product (1,2-anti), also characterized as an S_N2-like process, was observed to be more associative. This study highlights the importance of considering both S_N1- and S_N2-like ionizations when performing computational studies of nucleophilic substitutions.

The diastereoselective nucleophilic substitution of α-alkoxydithioacetals is proposed to arise from the difference in Gibbs

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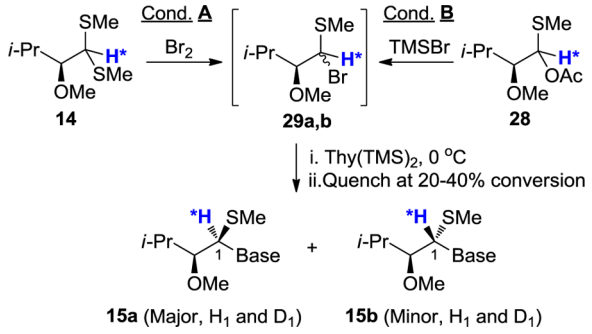
Table 7. Deuterium Secondary KIEs in Different Solvents at 0°C for the Nucleobase Substitution of Bromothioethers 29a,b (H* ≈ 50% ^{2}H-Enrichment)



		KIE (k_H/k_D) at 0 °C[a]			
		major (**15a**, 1,2-syn)		minor (**15b**, 1,2-anti)	
entry	solvent (conditions)	calcd	exp	calcd	exp
1	vacuum	1.28		1.16	
2	toluene (**B**, TMSBr)	1.24	1.13 ± 0.01	1.14	0.99 ± 0.04
3	THF (**A**, Br_2)	n.d.	1.18 ± 0.02	1.13	0.92 ± 0.03
4	THF (**B**, TMSBr)	n.d.	1.21 ± 0.02	1.13	1.03 ± 0.03
5	MeCN (**A**, Br_2)	n.d.	1.15 ± 0.04	1.14	n.d.

[a]See the Supporting Information and the Experimental Section (Tables 8 and 9) for more details concerning the KIE measurements and DFT calculations.

free energy between TS **A** (1,2-syn) and TS **D** (1,2-anti), both at the rate-determining and product-determining steps of these S_N2-like pathways. The established C1−C2 gauche conformational preference in these TS allows for an optimal stabilization of the thiacarbenium by sigma donation from the C2−H and the C2−R bonds. The free thiacarbenium ion was calculated to have the same gauche C1−C2 conformational preference. The counterion provides significant additional stabilization by interacting with the electron deficient thiacarbenium ion. The base addition occurs on the least hindered side of the thiacarbenium ion-pair species to minimize unfavorable interactions. Interactions between the iodide and the thiacarbenium substituents play an important role and have to be considered to rationalize the trends for 1,2-syn inductions obtained with 2,3-bis-alkoxydithioacetals. These substrates adopt conformations that can either destabilize TS **A**, to provide lower 1,2-syn inductions, or TS **D**, to furnish higher 1,2-syn induction. The model proposed herein correctly predicts trends in selectivity for acyclic and C2−C3 acetonides. The proper selection of protecting groups can therefore allow for a more optimal synthesis of nucleoside analogues from 2,3-anti-bis-alkoxydithioacetals. Polar solvents provided higher 1,2-syn selectivities, which is in agreement with the calculated more ionized, or less associative, nature of the syn-predictive TS **A**, as opposed to TS **D**. These observations are also consistent with the measured and calculated secondary kinetic isotope effects.

Overall, this work sheds light onto the pathway followed by α-alkoxyacetal substitutions with silylated nucleobases. These insights could help further improve diastereoselective N-glycosylations to generate nucleoside analogues more efficiently.

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. Tetrahydrofuran, dichloromethane, acetonitrile, toluene, and dimethyl sulfoxide were dried with 4 Å molecular sieves prior to use. The 4 Å molecular sieves (1−2 mm beads) were activated by heating at 180 °C for 48 h under a vacuum prior to adding to new bottles of solvent purged with argon. Commercially available reagents were used as received. Silylated thymine was prepared by known methods.[43] Flash chromatography was performed on Merck silica gel 60 (0.040−0.063 mm) using forced flow (flash chromatography) of the indicated solvent system or an automatic flash chromatography system. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) silica gel aluminum plates. Visualization was performed with UV short wavelength and/or revealed with ammonium molybdate or potassium permanganate solutions. ^{1}H NMR spectra were recorded at room temperature on 400 and 500 MHz NMR spectrometers as indicated. The data are reported as follows: chemical shift in ppm referenced to residual solvent ($CDCl_3$ δ 7.26 ppm), multiplicity (s = singlet, apps = apparent singlet, d = doublet, appd = apparent doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, appt = apparent triplet, td = triplet of doublets, apptd = apparent triplet doublets, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded at room temperature using 100.6 or 125 MHz as indicated. The data are reported as follows: chemical shift in ppm referenced to residual solvent ($CDCl_3$ δ 77.16 ppm). Infrared spectra were recorded on a FTIR spectrophotometer on a NaCl support, and signals are reported in cm^{-1}. Mass spectra were recorded either through electrospray ionization (ESI) or electron impact on an instrument operating at 70 eV, and FAB mass spectra were recorded with or without ionization. An Orbitrap mass analyzer was used for HRMS measurements. Optical rotations were measured at room temperature from the sodium D line (589 nm) using CH_2Cl_2 as solvent unless otherwise noted and calculated using the formula $\alpha_D = (100)\alpha_{obs}/(l\cdot(c))$, where c = (g of substrate/100 mL of solvent) and l = 1 dm.

Preparation of Dithioacetals 14, 16, 18, 20, 22, 24, and 26 (Table 1). *General Procedure A: Preparation of Bis(alkylthio)-methane Substrates.* To a solution of P_2O_5 in HPLC grade $CHCl_3$ at room temperature was added the corresponding alkylthiol and dimethoxymethane. The reaction mixture was refluxed overnight followed by cooling and addition of pyridine. Hexanes were added to dilute the mixture followed by filtration on silica gel and concentration *in vacuo*.

General Procedure B: Preparation of α-Hydroxy Dithioacetals. To a solution of bis(alkylthio)methane in THF at −78 °C was added *n*-BuLi. The reaction mixture was maintained for 5 min at −78 °C, followed by 30 min at −30 °C. After cooling to −78 °C, the appropriate

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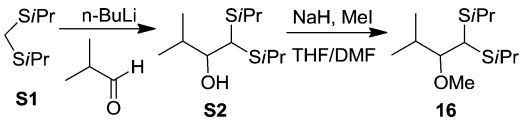
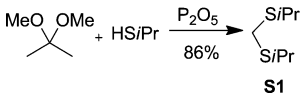
aldehyde was added and the reaction was stirred at 0 °C until complete by TLC. A 0.5 N HCl (10 mL) solution was added, and the aqueous layer was extracted with hexanes (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

General Procedure C: Preparation of α-Methoxy Dithioacetals. To a solution of the appropriate alcohol in an 85:15 mixture of THF/DMF at 0 °C was added NaH. MeI was added, and the reaction was stirred at room temperature until complete by TLC. A saturated aqueous NH_4Cl solution (20 mL) was added, and the aqueous layer was extracted with a mixture of diethyl ether:hexanes (50:50, 3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

*(±)-(2-Methoxy-3-methylbutane-1,1-diyl)bis(methylsulfane) (**14**).* Dithioacetal **14** has previously been reported in the literature by our laboratory.[4]

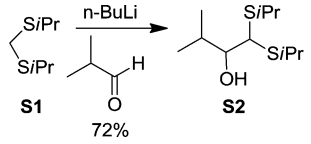


*Bis(isopropylthio)methane (**S1**).*[44]



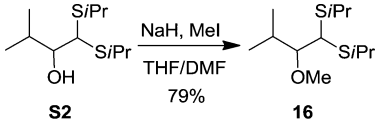
Following general procedure A, propane-2-thiol (3.0 mL, 32 mmol, 2.2 equiv) and dimethoxymethane (1.3 mL, 15 mmol, 1.0 equiv) were added to a solution of P_2O_5 (5.0 g, 18 mmol, 1.2 equiv) in $CHCl_3$ (40 mL, 0.30 M). Purification by flash chromatography (hexanes/EtOAc, 95:5) provided **S1** as a colorless oil (2.1 g, 86%): R_f = 0.8 (hexanes/EtOAc, 90:10). Formula: $C_7H_{16}S_2$. MW: 164.3319 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 1H), 3.21−3.10 (m, 1H), 1.29 (d, J = 6.7 Hz, 6H) ppm.

*(±)-1,1-Bis(isopropylthio)-3-methylbutan-2-ol (**S2**).*

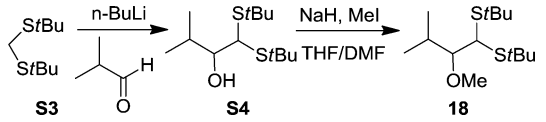


Following general procedure B, isobutyraldehyde (0.13 mL, 1.4 mmol, 1.0 equiv) was added to a solution of bis(*iso*-propylthio)methane **S1** (0.28 g, 1.7 mmol, 1.2 equiv), and *n*-BuLi (1.1 mL of 1.6 M solution in hexanes, 1.7 mmol, 1.2 equiv) in THF (7.0 mL, 0.20 M). Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **S2** as a colorless oil (0.24 g, 72%): R_f = 0.47 (hexanes/EtOAc, 90:10). Formula: $C_{11}H_{24}OS_2$. MW: 236.4377 g/mol. IR (neat) ν_{max} 3486, 2959 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98 (d, J = 5.4 Hz, 1H), 3.49 (as, 1H), 3.37 (dd, J = 6.2, 5.5 Hz, 1H), 3.22−3.05 (m, 2H), 2.15−2.02 (m, 1H), 1.34−1.29 (m, 12H), 0.99 (d, J = 4.9 Hz, 3H), 0.97 (d, J = 5.1 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 77.0, 54.9, 34.7, 34.5, 30.3, 24.0, 23.8, 23.35, 23.34, 19.5, 17.3 ppm. HRMS calcd for $C_{11}H_{24}OS_2Na$ [M + Na^+], 259.1161; found, 259.1167 (0.4 ppm).

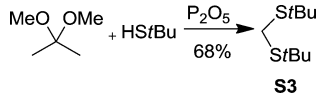
*(±)-(2-Methoxy-3-methylbutane-1,1-diyl)bis(isopropylsulfane) (**16**).*



Following the general procedure C, NaH (25 mg, 1.1 mmol, 1.3 equiv) and MeI (0.10 mL, 1.6 mmol, 2.0 equiv) were added to a solution of **S2** (0.19 g, 0.80 mmol, 1.0 equiv) in THF/DMF (3.4 mL:0.60 mL, 0.20 M). Purification by flash chromatography (hexanes/DCM, 90:10) resulted in **16** as a colorless oil (0.16 g, 79%): R_f = 0.44 (hexanes/DCM, 90:10). Formula: $C_{12}H_{26}OS_2$. MW: 250.4642 g/mol. IR (neat) ν_{max} 2959 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (d, J = 4.5 Hz, 1H), 3.54 (s, 3H), 3.20−3.06 (m, 2H), 3.04 (dd, J = 6.6, 4.6 Hz, 1H), 2.14−2.02 (m, 1H), 1.28−1.21 (m, 12H), 0.92 (d, J = 4.3 Hz, 3H), 0.90 (d, J = 4.5 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 90.6, 61.9, 52.2, 35.03, 34.96, 31.5, 23.8, 23.6, 23.41, 23.36, 20.1, 17.8 ppm. HRMS calcd for $C_{12}H_{26}OS_2Na$ [M + Na^+], 273.1317; found, 273.1322 (−0.4 ppm).

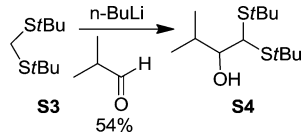


*Bis(tert-butylthio)methane (**S3**).*[45]



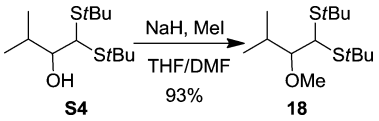
Following general procedure A, 2-methylpropane-2-thiol (2.0 mL, 18 mmol, 2.0 equiv) and dimethoxymethane (0.79 mL, 8.9 mmol, 1.0 equiv) were added to a solution of P_2O_5 (3.0 g, 11 mmol, 1.2 equiv) in $CHCl_3$ (30 mL, 0.30 M). Purification by flash chromatography (hexanes/EtOAc, 95:5) provided **S3** as a yellow oil (1.2 g, 68%): R_f = 0.53 (hexanes/EtOAc, 90:10). Formula: $C_9H_{20}S_2$. MW: 192.3851 g/mol. IR (neat) ν_{max} 2960 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 1H), 1.36 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 43.8, 31.1, 28.1 ppm

*(±)-1,1-Bis(tert-butylthio)-3-methylbutan-2-ol (**S4**).*

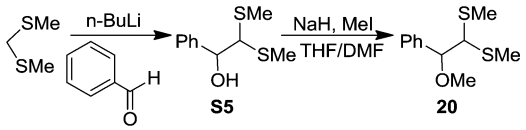


Following general procedure B, isobutyraldehyde (0.12 mL, 1.3 mmol, 1.3 equiv) was added to a solution of bis(*tert*-butylthio)methane **S3** (0.19 g, 0.96 mmol, 1.0 equiv) and *n*-BuLi (0.80 mL of 1.6 M solution in hexanes, 1.2 mmol, 1.2 equiv) in THF (5.0 mL, 0.20 M). Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **S4** as a colorless oil (0.14 g, 54%): R_f = 0.6 (hexanes/EtOAc, 90:10). Formula: $C_{13}H_{28}OS_2$. MW: 264.4908 g/mol. IR (neat) ν_{max} 3494, 2959 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (d, J = 3.0 Hz, 1H), 3.44 (td, J = 8.1, 3.0 Hz, 1H), 2.92 (d, J = 3.0 Hz, 1H), 2.25−2.12 (m, 1H), 1.41 (s, 9H), 1.40 (s, 9H), 1.03 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 79.8, 52.0, 45.5, 43.9, 32.0, 31.8, 30.2, 19.3, 19.2 ppm. MS (EI) m/z 250.1565 (11), 253.0752 (100), 255.0716 (16), 265.0747 (7, M + H^+).

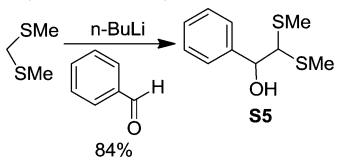
*(±)-(2-Methoxy-3-methylbutane-1,1-diyl)bis(tert-butylsulfane) (**18**).*



Following general procedure C, NaH (14 mg, 0.59 mmol, 1.2 equiv) and MeI (34 μL, 0.54 mmol, 1.1 equiv) were added to a solution of **S4** (0.13 g, 0.49 mmol, 1.0 equiv) in THF/DMF (1.7 mL/0.30 mL, 0.25 M). Purification by flash chromatography (hexanes/DCM, 90:10) resulted in **18** as a colorless oil (0.13 g, 93%): R_f = 0.59 (hexanes/DCM, 90:10). Formula: $C_{14}H_{30}OS_2$. MW: 278.5174 g/mol. IR (neat) ν_{max} 2959 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (d, J = 1.8 Hz, 1H), 3.64 (s, 3H), 3.16 (dd, J = 8.8, 1.7 Hz, 1H), 2.17−2.07 (m, 1H), 1.41 (s, 9H), 1.40 (s, 9H), 1.01 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 92.5, 62.1, 48.9, 45.3, 43.7, 32.0, 31.9, 31.7, 20.4, 19.5 ppm. HRMS calcd for $C_{14}H_{30}OS_2$ [M^+], 278.1738; found, 278.1732 (2.0 ppm).



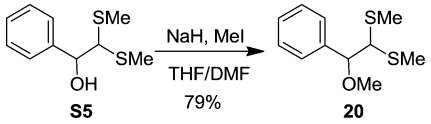
*(±)-2,2-Bis(methylthio)-1-phenylethanol (**S5**).*[46]



dx.doi.org/10.1021/jo502181a | J. Org. Chem. 2014, 79, 10504−10525

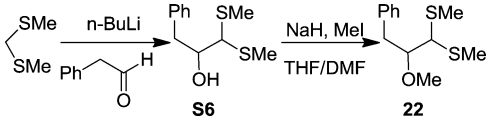
Following general procedure B, benzaldehyde (2.3 mL, 22 mmol, 1.2 equiv) was added to a solution of commercially available bis(methylthio)methane (1.9 mL, 19 mmol, 1.0 equiv) and *n*-BuLi (13 mL of 1.6 M solution in hexanes, 21 mmol, 1.1 equiv) in THF (117 mL, 0.16 M). Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **S5** (3.4 g, 84%): R_f = 0.4 (hexanes/EtOAc, 80:20). Formula: $C_{10}H_{14}OS_2$. MW: 214.3476 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.30 (m, 5H), 4.63 (d, J = 7.9 Hz, 1H), 3.84 (d, J = 7.9 Hz, 1H), 3.42 (as, 1H), 2.11 (s, 3H), 2.03 (s, 3H) ppm.

*(±)-(2-Methoxy-2-phenylethane-1,1-diyl)bis(methylsulfane) (**20**).*[46]



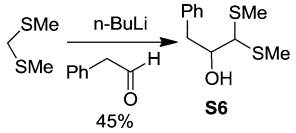
S5 **20**

Following general procedure C, NaH (0.49 g, 20 mmol, 1.3 equiv) and MeI (2 mL, 31 mmol, 2.0 equiv) were added to a solution of **S5** (3.4 g, 16 mmol, 1.0 equiv) in THF/DMF (67 mL/12 mL, 0.20 M). Purification by flash chromatography (hexanes/EtOAc, 95:5) resulted in **20** (2.8 g, 79%): R_f = 0.50 (hexanes/EtOAc, 95:5). Formula: $C_{11}H_{16}OS_2$. MW: 228.3741 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.30 (m, 5H), 4.39 (d, J = 6.3 Hz, 1H), 3.83 (d, J = 6.3 Hz, 1H), 3.27 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H) ppm.



S6 **22**

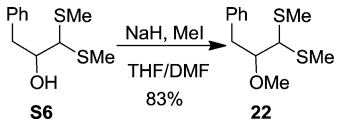
*(±)-1,1-Bis(methylthio)-3-phenylpropan-2-ol (**S6**).*



45% **S6**

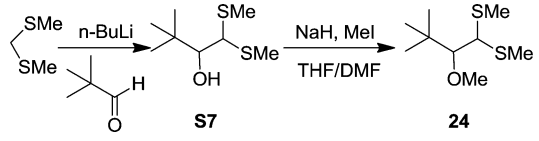
Following general procedure B, 2-phenylacetaldehyde (2.7 mL, 21 mmol, 1.2 equiv) was added to a solution of commercially available bis(methylthio)methane (1.8 mL, 18 mmol, 1.0 equiv) and *n*-BuLi (12 mL of 1.6 M solution in hexanes, 19 mmol, 1.1 equiv) in THF (110 mL, 0.20 M). Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **S6** as a colorless oil (1.8 g, 45%): R_f = 0.23 (hexanes/EtOAc, 90:10). Formula: $C_{11}H_{16}OS_2$. MW: 228.3741 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 3.96−3.90 (m, 1H), 3.58 (d, J = 6.6 Hz, 1H), 3.20 (dd, J = 13.8, 4.2 Hz, 1H), 2.89 (dd, J = 13.8, 7.7 Hz, 1H), 2.78 (s, 1H), 2.17 (s, 3H), 2.16 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.1, 129.6, 128.4, 126.6, 72.8, 61.1, 40.2, 14.7, 12.8 ppm. HRMS calcd for $C_{11}H_{16}OS_2Na$ [M + Na^+], 251.0535; found, 251.0535 (−1.9 ppm).

*(±)-(2-Methoxy-3-phenylpropane-1,1-diyl)bis(methylsulfane) (**22**).*



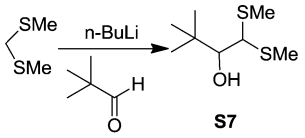
S6 **22**

Following general procedure C, NaH (0.23 g, 9.8 mmol, 1.3 equiv) and MeI (0.94 mL, 15 mmol, 2.0 equiv) were added to a solution of **S6** (1.7 g, 7.5 mmol) in THF/DMF (32 mL/6.0 mL, 0.20 M). Purification by flash chromatography (hexanes/EtOAc, 95:5) resulted in **22** as a colorless oil (1.5 g, 83%): R_f = 0.46 (hexanes/EtOAc, 90:10). Formula: $C_{12}H_{18}OS_2$. MW: 242.4077 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 5H), 3.76−3.70 (m, 1H), 3.66 (d, J = 4.0 Hz, 1H), 3.39 (s, 3H), 3.12 (dd, J = 13.6, 5.7 Hz, 1H), 3.03 (dd, J = 13.7, 7.0 Hz, 1H), 2.23 (s, 3H), 2.21 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.5, 129.5, 128.4, 126.3, 86.6, 58.7, 58.0, 38.2, 14.7, 14.4 ppm. HRMS calcd for $C_{12}H_{18}OS_2Na$ [M + Na^+], 265.0691; found, 265.0691 (−2.3 ppm).



S7 **24**

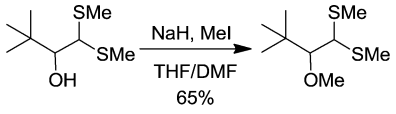
*(±)-3,3-Dimethyl-1,1-bis(methylthio)butan-2-ol (**S7**).*



48% **S7**

Following general procedure B, pivalaldehyde (1.4 mL, 12 mmol, 1.2 equiv) was added to a solution of commercially available bis(methylthio)methane (1.1 mL, 10 mmol, 1.0 equiv), and *n*-BuLi (8.7 mL of 1.3 M solution in hexanes, 11 mmol, 1.1 equiv) in THF (64 mL, 0.20 M). Purification by flash chromatography (hexanes/EtOAc, 95:5) provided **S7** as a colorless oil (0.96 g, 48%): R_f = 0.52 (hexanes/EtOAc, 80:20). Formula: $C_8H_{18}OS_2$. MW: 194.3579 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (d, J = 4.0 Hz, 1H), 3.41 (dd, J = 5.3, 4.0 Hz, 1H), 2.74 (d, J = 5.4 Hz, 1H), 2.18 (s, 3H), 2.16 (s, 3H), 1.01 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 80.4, 58.5, 35.8, 26.5, 15.0, 14.1 ppm. HRMS calcd for $C_8H_{18}OS_2Na$ [M + Na^+], 217.0691; found, 217.0699 (0.9 ppm).

*(±)-(2-Methoxy-3,3-dimethylbutane-1,1-diyl)bis(methylsulfane) (**24**).*



S7 **24**

Following general procedure C, NaH (88 mg, 3.7 mmol, 1.5 equiv) and MeI (0.31 mL, 4.9 mmol, 2.0 equiv) were added to a solution of **S7** (0.47 g, 2.5 mmol) in THF/DMF (10 mL/1.8 mL, 0.20 M). Purification by flash chromatography (hexanes/EtOAc, 95:5) resulted in **24** (0.33 g, 65%): R_f = 0.55 (hexanes/EtOAc, 95:5). Formula: $C_9H_{20}OS_2$. MW: 208.3845 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (d, J = 2.5 Hz, 1H), 3.54 (s, 3H), 3.17 (d, J = 2.5 Hz, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 0.97 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 93.0, 62.2, 57.5, 36.8, 26.6, 15.0, 14.7 ppm. HRMS calcd for $C_9H_{20}OS_2Na$ [M + Na^+], 231.0848; found, 231.0860 (3.1 ppm).

*(±)-tert-Butyldimethyl((3-methyl-1,1-bis(methylthio)butan-2-yl)oxy)silane (**26**).* Dithioacetal **26** has previously been reported in the literature by our laboratory.[4]

Preparation of Thioaminals 15, 17, 19, 21, 23, 25, and 27 (Table 1). *General Procedure D.* To a solution of the corresponding α-protected dithioacetal in anhydrous solvent at 0 °C were added silylated thymine 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. (N.B. Addition of silylated thymine as a solution in THF gave slightly higher 1,2-syn selectivity as compared to a solution in DCM.) 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-(2-Methoxy-3-methyl-1-(methylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**15a** and **15b**).* Following general procedure D, $Hg(OAc)_2$ (80 mg, 0.25 mmol, 1.05 equiv), silylated thymine (1.0 mL, 0.72 mmol, 3.0 equiv of a 0.70 M solution in DCM), and TMSOTf (0.25 mmol, 50 μL, 1.05 equiv) were added to a solution of **14** (46 mg, 0.24 mmol) in anhydrous THF (2.4 mL, 0.10 M) and stirred at room temperature. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 5:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 40:60) did not allow separation of the diastereomers and provided a mixture of **15a** and **15b** (53 mg, 82%) as a white solid: R_f = 0.39 (hexanes/EtOAc, 40:60). Formula: $C_{12}H_{20}N_2O_3S$. MW: 272.3638 g/mol. IR (neat) ν_{max} 3423, 2952, 1677 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H, isomer **a**), 8.60 (s, 1H, isomer **b**), 7.83 (s, 1H, isomer **a**), 7.75 (s, 1H, isomer **b**), 5.89 (s, 1H, isomer **b**), 5.74 (d, J = 3.3 Hz, 1H, isomer **a**), 3.52 (s, 3H, isomer **b**), 3.36 (s, 3H, isomer **a**), 3.18 (dd, J = 7.1, 2.9 Hz, 1H, isomer **b**), 3.02 (dd, J = 8.1, 3.3 Hz, 1H,

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isomer **a**), 2.09 (s, 3H, isomer **b**), 2.02 (s, 3H, isomer **a**), 1.98 (s, 3H, isomer **a**), 1.96 (s, 3H, isomer **b**), 1.95 (m, 1H, isomer **a**), 1.73−1.65 (m, 1H, isomer **b**), 1.03 (d, J = 1.5 Hz, 3H, isomer **a**), 1.02 (d, J = 1.4 Hz, 3H, isomer **a**), 0.99 (d, J = 6.7 Hz, 3H, isomer **b**), 0.93 (d, J = 6.7 Hz, 3H, isomer **b**) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.74 (isomer **a**), 163.66 (isomer **b**), 151.6 (isomer **b**), 151.2 (isomer **a**), 139.0 (isomer **b**), 138.0 (isomer **a**), 111.2 (isomer **b**), 110.8 (isomer **a**), 89.8 (isomer **a**), 77.4 (isomer **b**), 65.3 (isomer **a**), 63.2 (isomer **b**), 62.4 (isomer **b**), 61.7 (isomer **a**), 32.2 (isomer **a**), 31.7 (isomer **b**), 19.2 (isomer **b**), 19.1 (isomer **a**), 18.8 (isomer **a**), 18.6 (isomer **b**), 14.12 (isomer **a**), 14.08 (isomer **b**), 12.9 (isomer **b**), 12.7 (isomer **a**) ppm. HRMS calcd for $C_{12}H_{20}N_2O_3SNa$ [M + Na^+], 295.1087; found, 295.1087 (0.06 ppm).

*(±)-1-(1-(Isopropylthio)-2-methoxy-3-methylbutyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**17a** and **17b**).* Following general procedure D, silylated thymine (0.75 mL, 0.60 mmol, 3.0 equiv of a 0.80 M solution in DCM) and $Me_2S(SMe)BF_4$ (80 mg, 0.41 mmol, 2.05 equiv) were added to a solution of **16** (50 mg, 0.20 mmol) in anhydrous DCM (1.3 mL, 0.20 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 9:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 40:60) provided a mixture of **17a** (47 mg) and **17b** (4 mg) for a total yield of (51 mg) 84%.

17a: R_f = 0.35 (hexanes/EtOAc, 60:40). Formula: $C_{14}H_{24}N_2O_3S$. MW: 300.4170 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.85 (s, 1H), 5.87 (d, J = 2.7 Hz, 1H), 3.32 (s, 3H), 2.97 (dd, J = 8.7, 2.8 Hz, 1H), 2.87−2.74 (m, 1H), 1.97 (s, 3H), 2.00−1.93 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 1.00 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.4, 151.0, 138.7, 110.4, 90.6, 62.0, 61.8, 34.9, 32.2, 23.5, 23.2, 19.0, 18.9, 12.7 ppm. HRMS calcd for $C_{14}H_{25}N_2O_3S$ [M + H^+], 301.1580; found, 301.1581 (−1.7 ppm).

17b: R_f = 0.40 (hexanes/EtOAc, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.73 (s, 1H), 5.97 (d, J = 3.7 Hz, 1H), 3.51 (s, 3H), 3.15 (dd, J = 7.6, 3.7 Hz, 1H), 2.96−2.85 (m, 1H), 1.95 (s, 3H), 1.76−1.65 (m, 1H), 1.36 (d, J = 6.6 Hz, 3H), 1.21 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H) ppm.

*(±)-1-(1-(tert-Butylthio)-2-methoxy-3-methylbutyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**19a** and **19b**).* Following general procedure D, silylated thymine (0.45 mL, 0.36 mmol, 2.0 equiv of a 0.80 M solution in DCM) and I_2 (91 mg, 0.36 mmol, 2.0 equiv) were added to a solution of **18** (50 mg, 0.18 mmol) in anhydrous THF (2.0 mL, 0.10 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 9:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 50:50) provided **19a** (50 mg) and **19b** (2.3 mg) for a total yield of (52 mg) 92%.

19a: R_f = 0.39 (hexanes/EtOAc, 50:50). Formula: $C_{15}H_{26}N_2O_3S$. MW: 314.4435 g/mol. IR (neat) ν_{max} 3183, 2961, 1689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.87 (s, 1H), 5.89 (s, 1H), 3.29 (s, 3H), 2.91 (ad, J = 9.0 Hz, 1H), 2.06−1.97 (m, 1H), 1.96 (s, 3H), 1.26 (s, 9H), 1.00 (d, J = 6.7 Hz, 6H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.8, 150.8, 139.2, 109.9, 91.8, 61.8, 61.0, 44.2, 32.3, 31.2, 19.1, 18.8, 12.6 ppm. HRMS calcd for $C_{15}H_{26}N_2O_3S$: 314.1664; found, 314.1675 (−3.5 ppm).

19b: R_f = 0.44 (hexanes/EtOAc, 50:50). IR (neat) ν_{max} 3158, 2963, 1692, 1679 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.68 (s, 1H), 5.98 (d, J = 4.0 Hz, 1H), 3.50 (s, 3H), 3.13 (dd, J = 7.2, 4.0 Hz, 1H), 1.95 (s, 3H), 1.80−1.66 (m, 1H), 1.32 (s, 9H), 0.99 (d, J = 6.1 Hz, 3H), 0.97 (d, J = 6.2 Hz, 3H) ppm. HRMS calcd for $C_{15}H_{26}N_2O_3S$: 314.1664; found, 314.1651 (4.1 ppm).

*(±)-1-(2-Methoxy-1-(methylthio)-2-phenylethyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**21a** and **21b**).* Following general procedure D, silylated thymine (2.4 mL, 2.0 mmol, 3.0 equiv of a 0.82 M solution in DCM) and I_2 (0.30 g, 1.3 mmol, 2.0 equiv) were added to a solution of **20** (0.150 g, 0.66 mmol) in anhydrous THF (4.1 mL, 0.16 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 3:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided a mixture of **21a** and **21b** (0.18 g, 90%) as a white foam: R_f = 0.17 (hexanes/EtOAc, 60:40). Formula: $C_{15}H_{18}N_2O_3S$. MW: 306.3800 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H, isomer **a**), 8.54 (s, 1H, isomer **b**), 7.71 (s, 1H, isomer **b**), 7.71 (s, 1H, isomer **a**), 7.42−7.17 (m, 10H, isomer **a** and **b**), 5.91 (d, J = 4.1 Hz, 1H, isomer **b**), 5.78 (d, J = 3.7 Hz, 1H, isomer **a**), 4.56 (d, J = 4.5 Hz, 1H, isomer **b**), 4.46 (d, J = 3.7 Hz, 1H, isomer **a**), 3.29 (s, 3H, isomer **a**), 3.28 (s, 3H, isomer **b**), 2.04 (s, 3H, isomer **b**), 1.98 (s, 3H, isomer **b**), 1.95 (s, 3H, isomer **a**), 1.92 (s, 3H, isomer **a**) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.3 (isomer **a**), 164.2 (isomer **b**), 151.5 (isomer **a**), 151.4 (isomer **b**), 138.0 (isomer **a**), 137.7 (isomer **a**), 136.6 (isomer **b**), 136.5 (isomer **b**), 128.7 (isomer **b**), 128.63 (isomer **a**), 128.59 (isomer **b**), 128.5 (isomer **a**), 127.1 (isomer **a**), 126.8 (isomer **b**), 110.7 (isomer **b**), 110.6 (isomer **a**), 85.5 (isomer **a**), 84.9 (isomer **b**), 67.1 (isomer **a**), 65.3 (isomer **b**), 57.8 (isomer **b**), 57.7 (isomer **a**), 14.16 (isomer **a** or **b**), 14.14 (isomer **a** or **b**), 12.7 (isomer **b**), 12.6 (isomer **a**) ppm. HRMS calcd for $C_{15}H_{19}N_2O_3S$ [M + H^+], 307.1111; found, 307.1113 (−1.0 ppm).

*(±)-1-(2-Methoxy-1-(methylthio)-3-phenylpropyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**23a** and **23b**).* Following general procedure D, silylated thymine (1.6 mL, 1.2 mmol, 3.0 equiv of a 0.80 M solution in DCM) and I_2 (0.21 g, 0.83 mmol, 2.0 equiv) were added to a solution of **22** (0.10 g, 0.41 mmol) in anhydrous THF (2.6 mL, 0.16 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 2:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **23a** and **23b** (0.11 g, 83%) as a white foam.

23a (isolated with 10% of **23b**): R_f = 0.10 (hexanes/EtOAc, 60:40). Formula: $C_{16}H_{20}N_2O_3S$. MW: 320.4066 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.76 (s, 1H), 7.36−7.18 (m, 5H), 5.55 (d, J = 2.9 Hz, 1H), 3.64 (apptd, J = 7.1, 2.9 Hz, 1H), 3.25 (s, 3H), 3.10 (dd, J = 13.7, 6.7 Hz, 1H), 2.88 (dd, J = 13.7, 7.4 Hz, 1H), 2.00 (s, 3H), 1.93 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.3, 151.4, 138.0, 136.9, 129.2, 128.8, 126.9, 110.5, 85.1, 65.2, 58.9, 38.5, 14.1, 12.7 ppm. HRMS calcd for $C_{16}H_{20}N_2O_3SNa$: [M + Na^+], 343.1087; found, 343.1088 (−1.3 ppm).

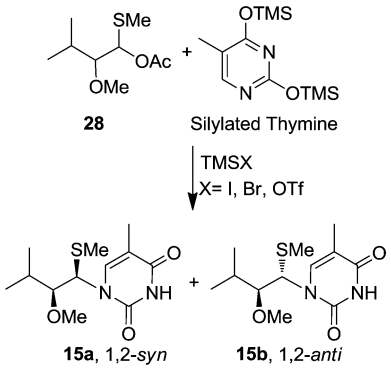
23b: R_f = 0.14 (hexanes/EtOAc, 60:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.69 (s, 1H), 7.31−7.17 (m, 5H), 5.79 (d, J = 3.8 Hz, 1H), 3.77 (ddd, J = 7.6, 4.6, 4.0 Hz, 1H), 3.26 (s, 3H), 2.83 (dd, J = 14.1, 4.7 Hz, 1H), 2.68 (dd, J = 14.1, 7.5 Hz, 1H), 2.06 (s, 3H), 1.95 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.9, 151.8, 138.6, 137.1, 129.5, 128.6, 126.8, 111.2, 85.1, 64.5, 60.4, 38.4, 14.2, 12.9 ppm. HRMS calcd for $C_{16}H_{20}N_2O_3SNa$: [M + Na^+], 343.1087; found, 343.1094 (0.5 ppm).

*(±)-1-(2-Methoxy-3,3-dimethyl-1-(methylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**25a** and **25b**).* Following general procedure D, silylated thymine (1.8 mL, 1.4 mmol, 3.0 equiv of a 0.80 M solution in DCM) and I_2 (0.24 g, 0.96 mmol, 2.0 equiv) were added to a solution of **24** (0.10 g, 0.48 mmol) in anhydrous THF (3.0 mL, 0.16 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer (>20:1). Purification by flash chromatography (hexanes/EtOAc, 60:40) provided **25a** (0.11 g, 81%) as a colorless oil: R_f = 0.30 (hexanes/EtOAc, 60:40). Formula: $C_{13}H_{22}N_2O_3S$. MW: 286.3904 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.80 (s, 1H), 5.79 (d, J = 2.6 Hz, 1H), 3.46 (s, 3H), 3.03 (d, J = 2.8 Hz, 1H), 1.99 (s, 3H), 1.96 (s, 3H), 1.04 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1, 151.2, 137.7, 111.4, 92.7, 65.1, 63.1, 36.7, 26.9, 13.8, 12.8 ppm. HRMS calcd for $C_{13}H_{23}N_2O_3S$: [M + H^+], 287.1424; found, 287.1426 (−1.3 ppm).

*(±)-1-(2-Methoxy-3,3-dimethyl-1-(methylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**27a** and **27b**).* Thioaminals **27a** and **27b** have previously been reported in the literature by our laboratory.[4]

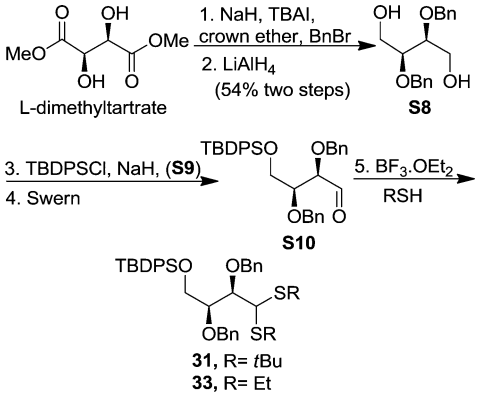
Preparation and Coupling on Thioacetate 28 (Table 2). *(±)-2-Methoxy-3-methyl-1-(methylthio)butyl Acetate (**28**).* To a solution of **14** (0.52 g, 2.7 mmol, 1.0 equiv) in anhydrous acetonitrile (26 mL, 0.10 M) at 0 °C was added $Hg(OAc)_2$ (1.0 g, 3.2 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 h, filtered on a pad of Celite, rinsed with diethyl ether, and concentrated *in vacuo*. ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a single diastereomer. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided **28** (0.45 g, 82%) as a colorless oil: R_f = 0.37 (hexanes/EtOAc, 90:10). Formula: $C_9H_{18}O_3S$. MW: 206.3024 g/mol. IR (neat) ν_{max} 2963, 1743 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (d, J = 3.5 Hz, 1H), 3.51 (s, 3H), 3.06 (dd, J = 6.7, 3.6 Hz, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 1.95−1.84 (m, 1H), 0.97 (at, J = 6.5 Hz, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 88.3, 83.3, 61.0, 31.0, 21.4, 19.8,

18.1, 14.7 ppm. HRMS calcd for $C_9H_{18}O_3SNa$ [M + Na^+], 229.0869; found, 229.0863 (−2.5 ppm).

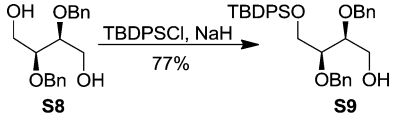


To a solution of **28** in anhydrous THF (0.10 M) at −20 °C was added TMSX (1.5 equiv). The reaction mixture was stirred at −10 °C for 1 h. Silylated thymine (3.0 equiv) was then added, and the reaction mixture was stirred at 0 °C overnight. Workup and purification were done according to general procedure D.

*Preparation of Dithioacetals **31**, **33**, **35**, **37**, **39**, and **41** (Table 3). Synthesis of 2,3-syn and 2,3-anti Bis-alkoxydithioacetals **31**, **33**, and **35**.*

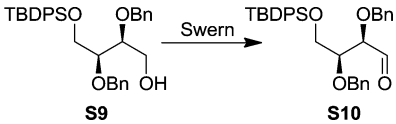


*(+)-(2S,3S)-2,3-Bis(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)butan-1-ol (**S9**).*



To a heterogeneous solution of NaH (0.21 g, 8.5 mmol, 1.0 equiv) in THF (15 mL, 0.60 M) at 0 °C was added dropwise (2*S*,3*S*)-2,3-bis(benzyloxy)butane-1,4-diol[47,48] **S8** (2.6 g, 8.5 mmol, 1.0 equiv) derived from L-dimethyltartrate. After stirring the reaction mixture at room temperature for 1 h, TBDPSCl (2.2 mL, 8.5 mmol, 1.00 equiv) was added and stirring continued for 3 h. A saturated solution of NH_4Cl (20 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 30 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 **S9** (3.5 g, 77%) as an oil: R_f = 0.26 (hexanes/EtOAc, 80:20). $[\alpha]^{25}_D$ + 6.9 (*c* 1.0, CH_2Cl_2). Formula: $C_{34}H_{40}O_4Si$. MW: 540.7645 g/mol. IR (neat) ν_{max} 3419 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77−7.67 (m, 4H), 7.49−7.27 (m, 16H), 4.70−4.49 (m, 4H), 3.96−3.64 (m, 6H), 2.24 (as, 1H), 1.09 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.41, 138.38, 135.78, 135.74, 133.3, 133.2, 129.93, 129.90, 128.54, 128.49, 128.08, 128.05, 127.91, 127.90, 127.86, 127.83, 80.1, 79.2, 73.1, 72.9, 63.0, 61.9, 27.0, 19.3 ppm. MS (ES, MS/MS TOF): *m*/*z* 541.2732 (90, M + H).

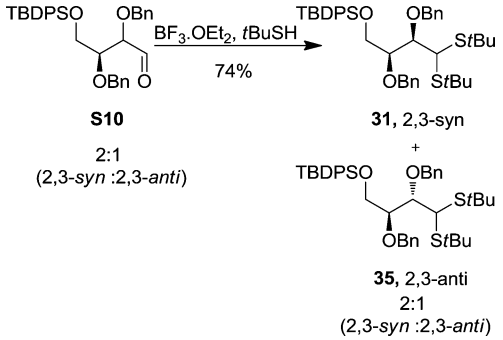
*(2R,3S)-2,3-Bis(benzyloxy)-4-(tert-butyldiphenylsilyloxy)butanal (**S10**).*



To a solution of $(COCl)_2$ (0.65 mL, 7.4 mmol, 1.2 equiv) in DCM (15 mL, 0.50 M) at −78 °C, DMSO (1.0 mL, 15 mmol, 2.0 equiv) was added dropwise. After stirring the solution for 15 min, **S9** (3.3 g, 6.1 mmol, 1.0 equiv) as a solution in DCM (15 mL, 0.40 M) was added and stirred for 1 h. NEt_3 (5.2 mL, 37 mmol, 6.0 equiv) was added, and the reaction mixture was stirred at −40 °C until determined complete based on TLC (2−3 h). A saturated solution of NH_4Cl (20 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was used for the next step.

S10: R_f = 0.47 (hexanes/EtOAc, 80:20). Formula: $C_{34}H_{38}O_4Si$. MW: 538.7486 g/mol. ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 1.2 Hz, 1H), 7.68−7.60 (m, 5H), 7.47−7.26 (m, 13H), 7.20−7.16 (m, 2H), 4.77 (d, *J* = 11.9 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.08−4.04 (m, 1H), 3.87−3.79 (m, 3H), 1.03 (s, 9H) ppm.

*(−)-((2S,3R)-2,3-Bis(benzyloxy)-4,4-bis(tert-butylthio)butoxy)(tert-butyl)diphenylsilane (**31**) and (+)-((2S,3S)-2,3-Bis(benzyloxy)-4,4-bis(tert-butylthio)butoxy)(tert-butyl)diphenylsilane (**35**).*



To a solution of epimerized aldehyde **S10** (this epimerization occurred while **S10** was left at room temperature for 12 h, providing a 2:1 mixture of 2,3-syn:2,3-anti) (2.0 g, 3.7 mmol, 1.0 equiv) in DCM (19 mL, 0.20 M) at −78 °C was added *t*BuSH (1.0 mL, 8.9 mmol, 2.4 equiv) and $BF_3{\cdot}OEt_2$ (0.56 mL, 4.5 mmol, 1.2 equiv). The reaction mixture was stirred at −78 °C for 5 h after which NEt_3 (0.62 mL, 4.5 mmol, 1.2 equiv) was added and stirring at −78 °C was continued for 5 min. A saturated solution of $NaHCO_3$ (10 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/DCM, 60:40) provided **31** and **35** (1.9 g, 74%) as an oil.

31: R_f = 0.30 (hexanes/EtOAc, 95:5). $[\alpha]^{25}_D$ −5.9 (*c* 1.0, CH_2Cl_2). Formula: $C_{42}H_{56}O_3S_2Si$. MW: 701.1077 g/mol. IR (neat) ν_{max} 3068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.68 (m, 4H), 7.46−7.24 (m, 16H), 4.96 (d, *J* = 11.4 Hz, 1H), 4.82 (d, *J* = 11.4 Hz, 1H), 4.69 (s, 2H), 4.23 (d, *J* = 1.8 Hz, 1H), 4.11−4.02 (m, 2H), 3.96 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.87 (dd, *J* = 11.1, 5.3 Hz, 1H), 1.35 (s, 9H), 1.29 (s, 9H), 1.09 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.1, 138.8, 135.9, 135.8, 133.7, 133.5, 129.74, 129.72, 128.27, 128.25, 128.2, 128.1, 127.766, 127.756, 127.5, 127.4, 83.2, 81.5, 75.0, 74.0, 64.5, 48.0, 45.2, 44.4, 31.9, 31.8, 27.1, 19.4 ppm. HRMS calcd for $C_{42}H_{56}O_3S_2SiNa$ [M + Na^+], 723.3332; found, 723.3339 (0.2 ppm).

35: R_f = 0.35 (hexanes/EtOAc, 95:5). $[\alpha]^{25}_D$ +9.4 (*c* 1.0, CH_2Cl_2). Formula: $C_{42}H_{56}O_3S_2Si$. MW: 701.1077 g/mol. IR (neat) ν_{max} 3068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.44−7.15 (m, 16H), 5.37 (d, *J* = 10.7 Hz, 1H), 4.84 (d, *J* = 10.8 Hz, 1H), 4.71 (as, 1H), 4.64 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 9.2 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.08−3.97 (m, 2H), 3.75 (d, *J* = 9.1 Hz, 1H), 1.47 (s, 9H), 1.36 (s, 9H), 1.09 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.73, 138.70, 135.9, 135.7, 133.5, 133.2, 129.72, 129.71, 128.244, 128.235, 128.0, 127.8, 127.6, 127.4, 127.2, 126.6, 83.1, 80.5, 75.7, 71.0, 60.3, 48.2, 46.0, 43.3, 32.0, 31.6, 26.9, 19.3 ppm. HRMS calcd for $C_{42}H_{56}O_3S_2SiNa$ [M + Na^+], 723.3332; found, 723.3327 (−1.5 ppm).

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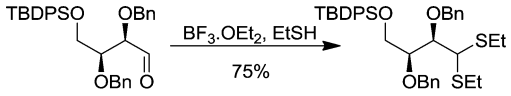
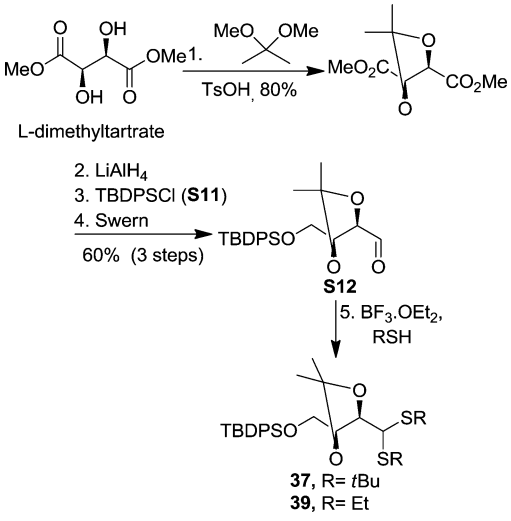
*(+)-((2S,3R)-2,3-Bis(benzyloxy)-4,4-bis(ethylthio)butoxy)(tert-butyl)diphenylsilane (**33**).*



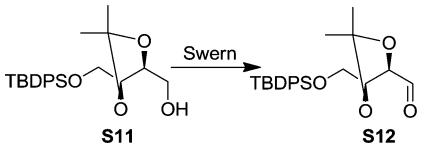
S10, 2,3-syn **33**, 2,3-syn

To a solution of aldehyde **S10** (0.50 g, 0.94 mmol, 1.0 equiv) in DCM (4.7 mL, 0.20 M) at −40 °C was added EtSH (0.17 mL, 2.4 mmol, 2.5 equiv) and $BF_3{\cdot}OEt_2$ (0.14 mL, 1.1 mmol, 1.2 equiv). The reaction mixture was stirred at −40 °C for 5 h after which NEt_3 (0.26 mL, 1.9 mmol, 2.0 equiv) was added and stirring at −40 °C was continued for 5 min. A saturated solution of $NaHCO_3$ (1 mL) was added, and the aqueous layer was extracted with ethyl acetate (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 **33** (0.45 g, 75%) as a colorless oil: R_f = 0.31 (hexanes/EtOAc, 90:10). $[\alpha]^{25}_D$ +2.0 (*c* 1.0, CH_2Cl_2). Formula: $C_{38}H_{48}O_3S_2Si$. MW: 645.0014 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.64 (m, 4H), 7.47−7.21 (m, 16H), 4.88 (d, *J* = 11.0 Hz, 1H), 4.76 (d, *J* = 11.0 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.10 (d, *J* = 5.7 Hz, 1H), 4.04−3.97 (m, 2H), 3.86 (dd, *J* = 10.8, 5.1 Hz, 1H), 3.79 (dd, *J* = 10.8, 4.6 Hz, 1H), 2.75−2.56 (m, 4H), 1.23 (t, *J* = 7.5 Hz, 3H), 1.19 (t, *J* = 7.5 Hz, 3H), 1.06 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.7, 138.6, 135.67, 135.64, 133.3, 133.2, 129.81, 129.76, 128.21, 128.20, 128.10, 128.09, 127.9, 127.80, 127.76, 127.5, 82.0, 80.8, 75.4, 73.3, 63.0, 53.0, 26.9, 25.5, 24.9, 19.2, 14.6, 14.5 ppm. HRMS calcd for $C_{38}H_{48}O_3S_2SiNa$ [M + Na^+], 667.2706; found, 667.2718 (0.9 ppm).

*Synthesis of 2,3-syn Bis-alkoxydithioacetals **37** and **39**.*



*(4R,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**S12**).*[49]

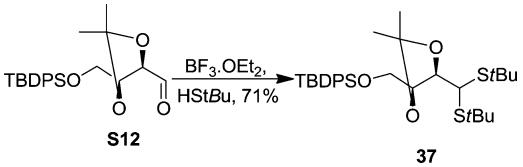


S11 **S12**

To a solution of $(COCl)_2$ (0.21 mL, 2.4 mmol, 1.2 equiv) in DCM (4.8 mL, 0.50 M) at −78 °C, DMSO (0.33 mL, 4.7 mmol, 2.4 equiv) was added dropwise. After stirring for 15 min, **S11** (0.78 g, 2.0 mmol, 1.0 equiv) was added as a solution in DCM (5.0 mL, 0.40 M) and stirred for 1 h. NEt_3 (1.6 mL, 12 mmol, 6.0 equiv) was added and the reaction kept at −40 °C until determined complete based on TLC (2−3 h). A saturated solution of NH_4Cl (10 mL) 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*. The crude reaction mixture was used for the next step.

S12: Formula: $C_{23}H_{30}O_4Si$. MW: 398.5674 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) 9.79 (d, *J* = 1.6 Hz, 1H), 7.74−7.64 (m, 5H), 7.46−7.36 (m, 5H), 4.44 (dd, *J* = 7.1, 1.6 Hz, 1H), 4.21−4.15 (m, 1H), 3.83 (dd, *J* = 9.6, 4.3 Hz, 2H), 1.49 (s, 3H), 1.42 (s, 3H), 1.06 (s, 9H) ppm.

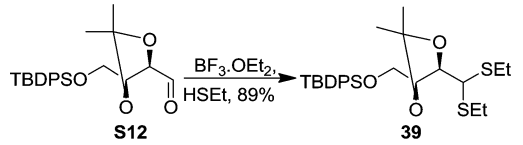
*(−)-(((4S,5R)-5-(Bis(tert-butylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(tert-butyl)diphenylsilane (**37**).*



S12 **37**

To a solution of aldehyde **S12** (50 mg, 0.13 mmol, 1.0 equiv) in DCM (0.63 mL, 0.20 M) at −60 °C was added *t*BuSH (31 μL, 0.28 mmol, 2.2 equiv) and $BF_3{\cdot}OEt_2$ (0.15 mL, 0.15 mmol, 1.2 equiv). The reaction mixture was stirred at −60 °C for 4 h, and NEt_3 was added (87 μL, 0.63 mmol, 5.0 equiv). After an additional 15 min of stirring at −60 °C, a saturated solution of $NaHCO_3$ (1 mL) 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/EtOAc, 90:10) provided **37** (49 mg, 71%) as a colorless oil: R_f = 0.3 (hexanes/EtOAc, 90:10). $[\alpha]^{25}_D$ −15.1 (*c* 1.0, CH_2Cl_2). Formula: $C_{31}H_{48}O_3S_2Si$. MW: 560.9265 g/mol. IR (neat) ν_{max} 2960 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.67 (m, 4H), 7.46−7.34 (m, 6H), 4.57 (dd, *J* = 7.4, 2.6 Hz, 1H), 4.22−4.17 (m, 1H), 4.07 (d, *J* = 2.6 Hz, 1H), 3.93 (dd, *J* = 11.1, 4.5 Hz, 1H), 3.86 (dd, *J* = 11.0, 3.7 Hz, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.41 (s, 9H), 1.37 (s, 9H), 1.07 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 135.82, 135.77, 133.4, 133.2, 129.84, 129.81, 127.81, 127.80, 109.8, 81.6, 79.7, 65.0, 47.4, 45.4, 44.5, 31.8, 31.7, 27.6, 27.3, 27.1, 19.4 ppm. HRMS calcd for $C_{31}H_{48}O_3S_2SiNa$ [M + Na^+], 583.2706; found, 583.2710 (−0.3 ppm).

*(−)-(((4S,5R)-5-(Bis(ethylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(tert-butyl)diphenylsilane (**39**).*



S12 **39**

To a solution of aldehyde **S12** (0.10 g, 0.25 mmol, 1.0 equiv) in DCM (1.3 mL, 0.20 M) at −60 °C was added EtSH (41 μL, 0.55 mmol, 2.2 equiv) and $BF_3{\cdot}OEt_2$ (38 μL, 0.30 mmol, 1.2 equiv). The reaction mixture was stirred at −60 °C for 3 h, and NEt_3 was added (0.17 mL, 1.3 mmol, 5.0 equiv). After an additional 15 min of stirring at −60 °C, a saturated solution of $NaHCO_3$ (1 mL) 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/EtOAc, 90:10) provided **39** (0.11 g, 89%) as a colorless oil: R_f = 0.3 (hexanes/EtOAc, 90:10). $[\alpha]^{25}_D$ −31.5 (*c* 1.0, CH_2Cl_2). Formula: $C_{27}H_{40}O_3S_2Si$. MW: 504.8202 g/mol. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71−7.67 (m, 4H), 7.45−7.36 (m, 6H), 4.40 (dd, *J* = 7.4, 4.8 Hz, 1H), 4.24−4.20 (m, 1H), 3.96 (d, *J* = 4.8 Hz, 1H), 3.90−3.83 (m, 2H), 2.80−2.64 (m, 4H), 1.47 (s, 3H), 1.42 (s, 3H), 1.25 (td, *J* = 10.6, 7.4 Hz, 6H), 1.07 (s, 9H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.801, 135.798, 133.29, 133.25, 129.90, 129.86, 127.86, 127.85, 109.8, 81.3, 79.9, 64.7, 53.6, 27.4, 27.3, 27.0, 25.5, 25.1, 19.4, 14.6, 14.5 ppm. HRMS calcd for $C_{27}H_{40}O_3S_2SiNa$ [M + Na^+], 527.2080; found, 527.2081 (0.2 ppm).

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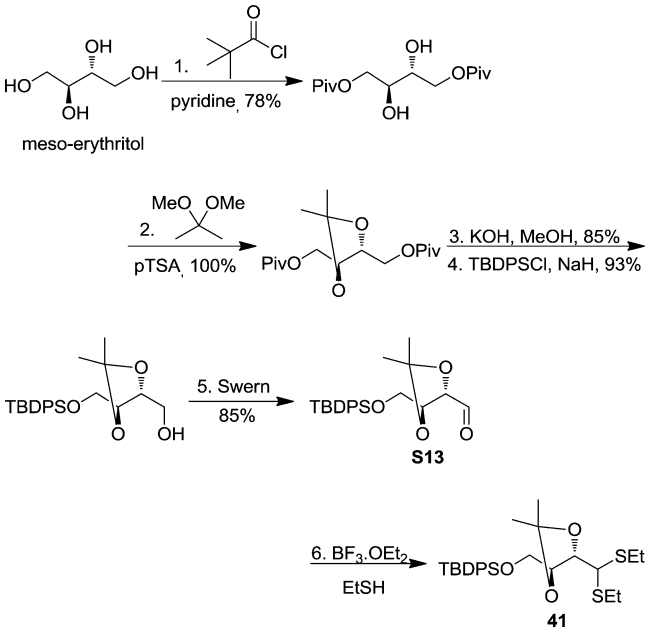
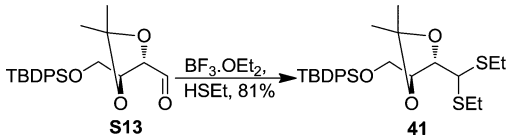
*Synthesis of 2,3-anti Bis-alkoxydithioacetals **41**.*



*(±)-(((4S,5R)-5-(Bis(ethylthio)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)(tert-butyl)diphenylsilane (**41**).*[50]



To a solution of aldehyde **S13**[51] (0.10 g, 0.25 mmol, 1.0 equiv) in DCM (1.6 mL, 0.16 M) at −40 °C was added EtSH (41 μL, 0.55 mmol, 2.2 equiv) and $BF_3{\cdot}OEt_2$ (0.30 mL, 0.30 mmol, 1.2 equiv, 1.0 M DCM). The reaction mixture was stirred at −40 °C for 3 h, and NEt_3 was added (0.17 mL, 1.3 mmol, 5.0 equiv). After an additional 15 min of stirring at −40 °C, a saturated solution of $NaHCO_3$ (3 mL) 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/EtOAc, 90:10) provided the known dithioacetal **41** (0.10 g, 81%): Formula: $C_{27}H_{40}O_3S_2Si$. MW: 504.8202 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.67 (m, 4H), 7.46−7.35 (m, 6H), 4.39 (dd, J = 7.6, 6.4 Hz, 1H), 4.32−4.26 (m, 1H), 4.14 (d, J = 7.6 Hz, 1H), 4.08 (dd, J = 10.8, 5.0 Hz, 1H), 3.92 (dd, J = 10.8, 5.0 Hz, 1H), 2.70−2.61 (m, 4H), 1.51 (s, 3H), 1.38 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H), 1.17 (t, J = 7.4 Hz, 3H), 1.08 (s, 9H) ppm.

*Preparation of Thioaminals **32**, **34**, **36**, **38**, **40**, and **42** (Table 3). 1-((1S,2R,3S)-2,3-Bis(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(tert-butylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**32a**) and 1-((1R,2R,3S)-2,3-Bis(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(tert-butylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**32b**).* Following general procedure D, silylated thymine (0.21 mL, 0.22 mmol, 3.0 equiv of a 1.0 M solution in DCM) and I_2 (36 mg, 0.14 mmol, 2.0 equiv) were added to a solution of **31** (50 mg, 0.071 mmol, 1.0 equiv) in anhydrous THF (0.70 mL, 0.10 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 15:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **32a** and **32b** (44 mg, 85%) as a colorless oil.

32a and **32b**: R_f = 0.22 (hexanes/EtOAc, 70:30). Formula: $C_{43}H_{52}N_2O_5SSi$. MW: 737.0339 g/mol. IR (neat) ν_{max} 3174, 1695, 1680 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, isomer **a**), 7.77−7.66 (m, 5H, isomer **a**), 7.45−7.26 (m, 14H, isomer **a**), 7.17−7.13 (m, 2H, isomer **a**), 6.18 (d, J = 4.2 Hz, 1H, isomer **b**), 5.98 (d, J = 2.9 Hz, 1H, isomer **a**), 4.88 (d, J = 11.4 Hz, 1H, isomer **b**), 4.80 (d, J = 11.2 Hz, 1H, isomer **a**), 4.70 (d, J = 11.6 Hz, 1H, isomer **a**), 4.65 (d, J = 11.5 Hz, 1H, isomer **a**), 4.48 (d, J = 11.8 Hz, 1H, isomer **b**), 4.36 (d, J = 11.3 Hz, 1H, isomer **a**), 4.23 (dd, J = 6.0, 4.1 Hz, 1H, isomer **b**), 4.02 (dd, J = 7.5, 2.9 Hz, 1H, isomer **a**), 3.94 (d, J = 3.8 Hz, 2H, isomer **a**), 3.84 (dd, J = 7.3, 3.9 Hz, 1H, isomer **a**), 1.80 (s, 1H, isomer **b**), 1.72 (s, 3H, isomer **a**), 1.16 (s, 9H, isomer **a**), 1.09 (s, 9H, isomer **a**) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.9, 150.1, 139.8, 138.6, 137.4, 135.93, 135.90, 133.35, 133.34, 129.83, 129.79, 128.5, 128.42, 128.40, 128.1, 127.84, 127.79, 127.78, 127.6, 109.3, 82.2, 81.9, 75.3, 73.4, 63.2, 59.0, 44.6, 31.0, 27.0, 19.4, 12.5 ppm. HRMS calcd for $C_{43}H_{53}N_2O_5SSi$ [M + H$^+$], 737.3439; found, 737.3455 (1.4 ppm).

*1-((1S,2R,3S)-2,3-Bis(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(ethylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**34a**) and 1-((1R,2R,3S)-2,3-Bis(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(ethylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**34b**).* Following general procedure D, silylated thymine (0.69 mL, 0.62 mmol, 2.0 equiv of a 0.90 M solution in DCM) and I_2 (0.16 g, 0.62 mmol, 2.0 equiv) were added to a solution of **33** (0.20 g, 0.31 mmol, 1.0 equiv) in anhydrous THF (3.1 mL, 0.10 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 14:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **34a** and **34b** (0.19 g, 84%) as a colorless oil.

34a and **34b**: R_f = 0.31 (hexanes/EtOAc, 60:40). Formula: $C_{41}H_{48}N_2O_5SSi$. MW: 708.9807 g/mol. IR (neat) ν_{max} 3182, 1684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.70 (m, 5H, isomer **a**), 7.64 (s, 1H, isomer **a**), 7.46−7.27 (m, 14H, isomer **a**), 7.20−7.16 (m, 2H, isomer **a**), 6.15 (d, J = 4.3 Hz, 1H, isomer **b**), 5.94 (s, 1H, isomer **a**), 4.86 (d, J = 11.0 Hz, 1H, isomer **b**), 4.80 (d, J = 11.2 Hz, 1H, isomer **a**), 4.68−4.51 (m, 2H, isomer **a**), 4.42 (d, J = 11.1 Hz, 1H, isomer **a**), 4.20 (dd, J = 5.8, 4.8 Hz, 1H, isomer **b**), 4.03 (dd, J = 6.9, 3.3 Hz, 1H, isomer **a**), 3.92 (dd, J = 4.2, 1.0 Hz, 2H, isomer **a**), 3.77 (dd, J = 10.8, 4.1 Hz, 1H, isomer **a**), 3.57 (dd, J = 10.1, 4.3 Hz, 1H, isomer **b**), 2.51−2.43 (m, 2H, isomer **b**), 2.36 (q, J = 7.4 Hz, 2H, isomer **a**), 1.79 (s, 3H, isomer **b**), 1.72 (s, 3H, isomer **a**), 1.14 (t, J = 7.4 Hz, 3H, isomer **a**), 1.09 (s, 9H, isomer **a**) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.2, 150.7, 138.9, 138.4, 137.3, 135.81, 135.80, 133.22, 133.17, 129.84, 129.79, 128.45, 128.44, 128.36, 128.35, 128.1, 127.82, 127.77, 127.6, 110.0, 81.6, 81.2, 75.3, 73.4, 63.1, 27.0, 25.1, 19.3, 14.7, 14.3, 12.5 ppm. HRMS calcd for $C_{41}H_{49}N_2O_5SSi$ [M + H$^+$], 709.3126; found, 709.3147 (2.2 ppm).

*(+)-1-((1R,2S,3S)-2,3-Bis(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(tert-butylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**36a**) and (−)-1-((1S,2S,3S)-2,3-Bis(benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(tert-butylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**36b**).* Following general procedure D, silylated thymine (0.21 mL, 0.21 mmol, 3.0 equiv of a 1.0 M solution in DCM) and I_2 (36 mg, 0.14 mmol, 2.0 equiv) were added to a solution of **35** (50 mg, 0.071 mmol, 1.0 equiv) in anhydrous THF (0.70 mL, 0.10 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 2:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **36a** and **36b** (43 mg, 82%) as a colorless oil.

36a: R_f = 0.18 (hexanes/EtOAc, 70:30). $[\alpha]^{25}_D$ +42.5 (c 1.0, CH_2Cl_2). Formula: $C_{43}H_{52}N_2O_5SSi$. MW: 737.0339 g/mol. IR (neat) ν_{max} 3176, 1682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.75 (d, J = 1.1 Hz, 1H), 7.65−7.61 (m, 4H), 7.42−7.26 (m, 12H), 7.19−7.12 (m, 4H), 6.36 (d, J = 2.3 Hz, 1H), 4.76 (d, J = 11.1 Hz, 1H), 4.64 (d, J = 11.9 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 4.15 (dd, J = 8.5, 2.3 Hz, 1H), 4.08 (dd, J = 11.8, 1.8 Hz, 1H), 3.92 (dd, J = 11.8, 3.3 Hz, 1H), 3.81−3.76 (m, 1H), 1.75 (s, 3H), 1.16 (s, 9H), 1.06 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1, 150.3, 139.7, 138.4, 137.3, 136.0, 135.8, 133.4, 132.9, 129.9, 129.8, 128.6, 128.4, 128.1, 127.9, 127.80, 127.76, 127.2, 126.5, 109.6, 82.2, 80.6, 75.1, 71.3, 61.2, 60.6, 44.5, 31.1, 27.1, 19.4, 12.6 ppm. HRMS calcd for $C_{43}H_{53}N_2O_5SSi$ [M + H$^+$], 737.3444; found, 737.3453 (1.2 ppm).

36b: R_f = 0.22 (hexanes/EtOAc, 70:30). $[\alpha]^{25}_D$ −4.2 (c 1.0, CH_2Cl_2). Formula: $C_{43}H_{52}N_2O_5SSi$. MW: 737.0339 g/mol. IR (neat) ν_{max} 3173, 1676 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.66−7.60 (m, 4H), 7.58 (d, J = 1.2 Hz, 1H), 7.43−7.37 (m, 2H), 7.34−7.27 (m, 12H), 7.24−7.20 (m, 2H), 6.29 (d, J = 2.3 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 4.71 (d, J = 11.0 Hz, 1H), 4.53 (d, J = 10.7 Hz, 1H), 4.42 (d, J = 10.7 Hz, 1H), 4.09 (dd, J = 7.2, 2.3 Hz, 1H), 4.00 (dd, J = 11.3, 3.6 Hz, 1H), 3.84 (dd, J = 11.3, 4.4 Hz, 1H), 3.46−3.40 (m, 1H), 1.67 (s, 3H),

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1.32 (s, 9H), 1.06 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.6, 150.7, 140.6, 138.3, 137.6, 135.9, 135.7, 133.4, 133.1, 129.90, 129.89, 128.6, 128.4, 128.0, 127.94, 127.89, 127.88, 127.83, 127.7, 109.3, 82.4, 79.6, 74.6, 72.6, 62.1, 58.3, 45.4, 31.1, 27.1, 19.4, 12.5 ppm. HRMS calcd for $C_{43}H_{53}N_2O_5SSi$ [M + H$^+$], 737.3444; found, 737.3451 (0.9 ppm).

*(−)-1-((S)-((4R,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(tert-butylthio) methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**38a**) and (+)-1-((R)-((4R,5S)-5-(((tert-Butyldiphenylsilyl) oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(tert-butylthio)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**38b**).* Following general procedure D, silylated thymine (0.25 mL, 0.23 mmol, 2.0 equiv of a 0.95 M solution in DCM) and I_2 (59 mg, 0.23 mmol, 2.0 equiv) were added to a solution of **37** (65 mg, 0.12 mmol, 1.0 equiv) in anhydrous THF (1.2 mL, 0.10 M). ^{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, 80:20) provided **38a** and **38b** (51 mg, 74%) as a colorless oil.

38a: R_f = 0.20 (hexanes/EtOAc, 70:30). $[\alpha]^{25}_D$ −84.1 (*c* 1.0, CH_2Cl_2). Formula: $C_{32}H_{44}N_2O_5SSi$. MW: 596.8527 g/mol. IR (neat) ν_{max} 3184, 1692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.72−7.64 (m, 5H), 7.46−7.35 (m, 6H), 5.98 (d, *J* = 2.5 Hz, 1H), 4.31 (dd, *J* = 7.5, 2.5 Hz, 1H), 4.24−4.19 (m, 1H), 3.80−3.72 (m, 2H), 1.96 (s, 3H), 1.48 (s, 3H), 1.35 (s, 3H), 1.29 (s, 9H), 1.06 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.9, 150.3, 139.0, 135.79, 135.76, 133.0, 132.95, 129.91, 129.90, 127.90, 127.88, 110.74, 110.68, 81.7, 79.6, 64.0, 59.7, 44.3, 31.1, 27.4, 27.1, 26.9, 19.3, 12.8 ppm. HRMS calcd for $C_{32}H_{45}N_2O_5SSi$ [M + H$^+$], 597.2813; found, 597.2799 (−3.3 ppm).

38b: R_f = 0.18 (hexanes/EtOAc, 70:30). $[\alpha]^{25}_D$ +26.6 (*c* 1.0, CH_2Cl_2). Formula: $C_{32}H_{44}N_2O_5SSi$. MW: 596.8527 g/mol. IR (neat) ν_{max} 3187, 1695 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.72−7.67 (m, 5H), 7.61 (d, *J* = 1.2 Hz, 1H), 7.47−7.35 (m, 5H), 5.97 (d, *J* = 4.7 Hz, 1H), 4.42 (dd, *J* = 7.3, 4.7 Hz, 1H), 3.92−3.81 (m, 2H), 3.80−3.75 (m, 1H), 1.95 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.31 (s, 9H), 1.08 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.8, 150.9, 139.2, 135.80, 135.78, 133.19, 133.15, 130.0, 129.9, 127.88, 127.85, 110.34, 110.33, 79.9, 79.0, 63.2, 57.5, 45.4, 31.1, 31.0, 27.3, 27.0, 19.5, 12.6 ppm. HRMS calcd for $C_{32}H_{45}N_2O_5SSi$ [M + H$^+$], 597.2813; found, 597.2822 (0.6 ppm).

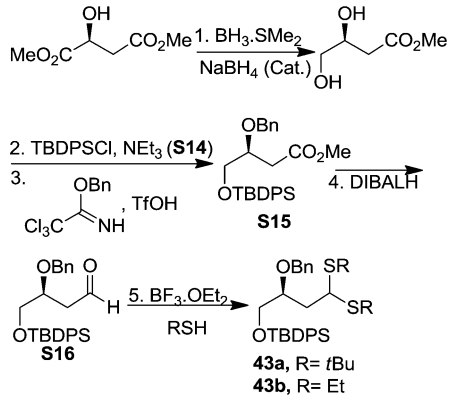
*(−)-1-((S)-((4R,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(ethylthio)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**40a**) and (+)-1-((R)-((4R,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-(ethylthio)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**40b**).* Following general procedure D, silylated thymine (2.2 mL, 2.0 mmol, 2.4 equiv of a 0.95 M solution in DCM) and I_2 (0.51 g, 2.0 mmol, 2.4 equiv) were added to a solution of **39** (0.44 g, 0.86 mmol, 1.0 equiv) in anhydrous THF (8.7 mL, 0.10 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a 4:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 70:30) provided **40a** and **40b** (0.34 g, 70%) as a colorless oil.

40a: R_f = 0.22 (hexanes/EtOAc, 70:30). $[\alpha]^{25}_D$ −74.4 (*c* 1.0, CH_2Cl_2). Formula: $C_{30}H_{40}N_2O_5SSi$. MW: 568.7995 g/mol. IR (neat) ν_{max} 3192, 1690 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.71−7.64 (m, 5H), 7.46−7.35 (m, 6H), 6.03 (d, *J* = 1.3 Hz, 1H), 4.24 (s, 2H), 3.79−3.76 (m, 2H), 2.62−2.45 (m, 2H), 1.96 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.24 (t, *J* = 7.4 Hz, 3H), 1.06 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.3, 151.1, 138.1, 135.70, 135.65, 132.9, 132.8, 129.9, 129.8, 127.9, 127.8, 111.5, 110.7, 80.8, 79.4, 63.7, 61.3, 27.3, 26.9, 26.8, 24.9, 19.2, 14.6, 12.8 ppm. HRMS calcd for $C_{30}H_{40}N_2O_5SSiNa$ [M + Na$^+$], 591.2319; found, 591.2324 (−0.2 ppm).

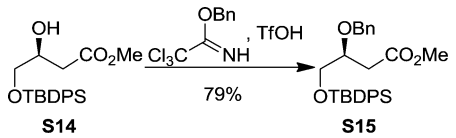
40b: R_f = 0.17 (hexanes/EtOAc, 70:30). $[\alpha]^{25}_D$ +45.6 (*c* 1.0, CH_2Cl_2). Formula: $C_{30}H_{40}N_2O_5SSi$. MW: 568.7995 g/mol. IR (neat) ν_{max} 3192, 1694 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.73−7.63 (m, 5H), 7.48−7.36 (m, 6H), 5.88 (d, *J* = 4.2 Hz, 1H), 4.39−4.33 (m, 1H), 3.89−3.76 (m, 3H), 2.59−2.43 (m, 2H), 1.95 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H), 1.26 (t, *J* = 7.4 Hz, 3H), 1.09 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.8, 151.5, 138.5, 135.83, 135.81, 133.14, 133.11, 130.0, 129.9, 127.89, 127.86, 110.7, 110.6, 79.0, 78.8, 63.2, 59.0, 27.3, 26.99, 26.98, 25.5, 19.4, 14.6, 12.7 ppm. HRMS calcd for $C_{30}H_{40}N_2O_5SSiNa$ [M + Na$^+$], 591.2319; found, 591.2338 (2.2 ppm).

*(±)-1-((S)-((4R,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)(ethylthio)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**42a**).* Following general procedure D, silylated thymine (0.25 mL, 0.23 mmol, 2.0 equiv of a 0.95 M solution in DCM) and I_2 (59 mg, 0.23 mmol, 2.0 equiv) were added to a solution of **41** (59 mg, 0.12 mmol, 1.0 equiv) in anhydrous THF (1.2 mL, 0.10 M). ^{1}H NMR spectroscopic analysis of the unpurified product indicated the formation of a >20:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 60:40) provided **42a** (53 mg, 81%) as a colorless oil: R_f = 0.11 (hexanes/EtOAc, 95:5). Formula: $C_{30}H_{40}N_2O_5SSi$. MW: 568.7995 g/mol. IR (neat) ν_{max} 3189, 1691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.77−7.66 (m, 5H), 7.47−7.35 (m, 6H), 6.26 (d, *J* = 1.3 Hz, 1H), 4.45 (dd, *J* = 6.9, 1.2 Hz, 1H), 4.40−4.30 (m, 2H), 3.98 (td, *J* = 4.5, 1.1 Hz, 1H), 2.44−2.34 (m, 2H), 1.97 (s, 3H), 1.53 (s, 3H), 1.30 (s, 3H), 1.14 (t, *J* = 7.4 Hz, 3H), 1.10 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1, 150.9, 138.5, 135.79, 135.78, 133.2, 133.1, 129.92, 129.91, 127.85, 127.82, 111.2, 109.7, 79.9, 77.2, 62.0, 60.1, 26.9, 26.0, 24.1, 24.6, 19.2, 14.3, 12.9 ppm. HRMS calcd for $C_{30}H_{40}N_2O_5SSiNa$ [M + Na$^+$], 591.2319; found, 591.2306 (−3.2 ppm).

*Preparation of Dithioacetals **43** (Figure 3).*



*(−)-(S)-Methyl 3-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-butanoate (**S15**).*



To a solution of **S14**[52−54] (0.65 g, 1.8 mmol, 1.0 equiv) in a 2:1 mixture of cyclohexane:DCM (8.8 mL, 0.20 M) at 0 °C was added benzyl 2,2,2-trichloroacetimidate (0.49 mL, 2.6 mmol, 2.6 equiv) and TfOH (16 μL, 0.18 mmol, 0.10 equiv). The reaction mixture was stirred at 0 °C for 12 h. A saturated solution of $NaHCO_3$ (10 mL) 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, 90:10) provided **S15** (0.51 g, 79%) as a colorless oil: R_f = 0.18 (hexanes/EtOAc, 90:10). $[\alpha]^{25}_D$ −19.2 (*c* 1.0, CH_2Cl_2). Formula: $C_{28}H_{34}O_4Si$. MW: 462.6527 g/mol. IR (neat) ν_{max} 2952, 1740 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.46−7.23 (m, 11H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 1H), 4.06−3.99 (m, 1H), 3.76 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.66 (s, 3H), 3.65 (dd, *J* = 15.4, 4.8 Hz, 1H), 2.70 (dd, *J* = 15.6, 4.6 Hz, 1H), 2.60 (dd, *J* = 15.6, 8.2 Hz, 1H), 1.06 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 138.5, 135.71, 135.68, 133.4, 133.3, 129.84, 129.83, 128.4, 127.84, 127.821, 127.819, 127.6, 76.8, 72.6, 65.4, 51.7, 37.5, 26.9, 19.3 ppm. HRMS calcd for $C_{28}H_{34}O_4SiNa$ [M + Na$^+$], 485.2119; found, 485.2119 (0.15 ppm).

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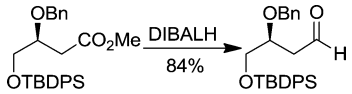
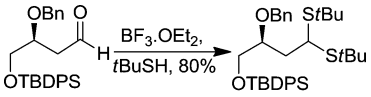
*(−)-(S)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)butanal (**S16**).*[55]



S15 **S16**

To a solution of **S15** (60 mg, 0.13 mmol, 1.0 equiv) in DCM (1.3 mL, 0.10 M) at −78 °C was added DIBALH (0.33 mL of a 1.0 M solution in hexanes, 0.33 mmol, 2.5 equiv) dropwise. The reaction mixture was stirred at −78 °C for 20 min, and 125 μL of methanol was added. After stirring at 25 °C, an equivalent volume of water was added. The aqueous layer was extracted with diethyl ether (3 × 3 mL) and washed with a 1.0 N HCl solution (2 mL) and a saturated solution of $NaHCO_3$ (2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexanes/EtOAc, 90:10) provided the known aldehyde **S16** (47 mg, 84%) as a colorless oil: $[\alpha]^{25}_D$ −19.0 (*c* 1.0, CH_2Cl_2). Formula: $C_{27}H_{32}O_3Si$. MW: 432.6267 g/mol. ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, *J* = 2.1 Hz, 1H), 7.70−7.63 (m, 4H), 7.47−7.24 (m, 11H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.08−4.00 (m, 1H), 3.80 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.71 (dd, *J* = 10.7, 5.5 Hz, 1H), 2.72 (d, *J* = 2.0 Hz, 1H), 2.70 (d, *J* = 2.1 Hz, 1H), 1.07 (s, 9H) ppm.

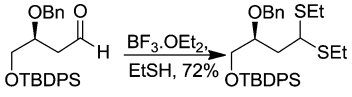
*(−)-(S)-(2-(Benzyloxy)-4,4-bis(tert-butylthio)butoxy)(tert-butyl)-diphenylsilane (**43a**).*



S16 **43a**

To a solution of aldehyde **S16** (0.10 g, 0.23 mmol, 1.0 equiv) in DCM (2.3 mL, 0.10 M) at −40 °C was added *t*BuSH (65 μL, 0.58 mmol, 2.5 equiv) and $BF_3{\cdot}OEt_2$ (35 μL, 0.28 mmol, 1.2 equiv). The reaction mixture was stirred at −40 °C for 3 h, and NEt_3 was added (64 μL, 0.46 mmol, 2.0 equiv). After an additional 15 min of stirring at −40 °C, a saturated solution of $NaHCO_3$ (1 mL) 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, 95:5) provided **43a** (0.11 g, 80%) as a colorless oil: R_f = 0.40 (hexanes/EtOAc, 95:5). $[\alpha]^{25}_D$ −18.8 (*c* 1.0, CH_2Cl_2). Formula: $C_{35}H_{50}O_2S_2Si$. MW: 594.9858 g/mol. IR (neat) ν_{max} 2960 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.64 (m, 4H), 7.46−7.28 (m, 11H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.17 (dd, *J* = 10.7, 2.9 Hz, 1H), 3.89−3.82 (m, 1H), 3.76−3.66 (m, 2H), 2.42−2.32 (m, 1H), 1.99−1.89 (m, 1H), 1.37 (s, 9H), 1.35 (s, 9H), 1.05 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 139.3, 135.80, 135.78, 133.6, 133.5, 129.78, 129.76, 128.3, 127.81, 127.78, 127.4, 127.3, 78.3, 71.9, 65.5, 45.6, 44.6, 44.0, 42.8, 31.9, 31.6, 27.0, 19.4 ppm. HRMS calcd for $C_{35}H_{50}O_2S_2SiNa$ [M + Na^+], 617.2914; found, 617.2933 (2.2 ppm).

*(−)-(S)-(2-(Benzyloxy)-4,4-bis(ethylthio)butoxy)(tert-butyl)-diphenylsilane (**43b**).*



S16 **43b**

To a solution of aldehyde **S16** (0.21 g, 0.47 mmol, 1.0 equiv) in DCM (2.9 mL, 0.16 M) at −40 °C was added EtSH (77 μL, 1.0 mmol, 2.2 equiv) and $BF_3{\cdot}OEt_2$ (72 μL, 0.57 mmol, 1.2 equiv). The reaction mixture was stirred at −40 °C for 3 h, and NEt_3 was added (0.33 mL, 2.4 mmol, 5.0 equiv). After an additional 15 min of stirring at −40 °C, a saturated solution of $NaHCO_3$ (3 mL) 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/EtOAc, 95:5) provided **43b** (0.18 g, 72%) as a colorless oil: R_f = 0.19 (hexanes/EtOAc, 95:5). $[\alpha]^{25}_D$ −26.0 (*c* 1.0, CH_2Cl_2). Formula: $C_{31}H_{42}O_2S_2Si$. MW: 538.8795 g/mol. IR (neat) ν_{max} 2960 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.66 (m, 4H), 7.47−7.26 (m, 11H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 3.99 (dd, *J* = 9.7, 5.2 Hz, 1H), 3.95−3.88 (m, 1H), 3.77 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.65 (dd, *J* = 10.6, 5.2 Hz, 1H), 2.71−2.49 (m, 4H), 2.10−1.94 (m, 2H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.23 (t, *J* = 7.4 Hz, 3H), 1.07 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 138.9, 135.72, 135.70, 133.43, 133.36, 129.8, 128.4, 127.86, 127.85, 127.81, 127.80, 127.6, 77.5, 72.6, 65.9, 47.8, 38.8, 26.9, 24.3, 23.4, 19.3, 14.60, 14.56 ppm. HRMS calcd for $C_{31}H_{42}O_2S_2SiNa$ [M + Na^+], 561.2288; found, 561.2311 (3.2 ppm).

*Preparation of Thioaminals **44** and **45** (Figure 3). (−)-1-((1R,3S)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(tert-butylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione and (−)-1-((1S,3S)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(tert-butylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**44a** and **44b**).* Following general procedure D, silylated thymine (1.3 mL, 1.3 mmol, 3.0 equiv of a 1.0 M solution in DCM) and I_2 (0.21 g, 0.84 mmol, 2.0 equiv) were added to a solution of **43a** (0.25 g, 0.42 mmol, 1.0 equiv) in anhydrous THF (4.2 mL, 0.10 M). ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **44a** and **44b** (0.20 g, 76%) as a colorless oil.

44a: R_f = 0.09 (hexanes/EtOAc, 80:20). $[\alpha]^{25}_D$ −41.1 (*c* 1.0, CH_2Cl_2). Formula: $C_{36}H_{46}N_2O_4SSi$. MW: 630.9119 g/mol. IR (neat) ν_{max} 3180, 1683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.70−7.63 (m, 4H), 7.47−7.20 (m, 12H), 6.14 (t, *J* = 7.2 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.32 (d, *J* = 11.5 Hz, 1H), 3.76 (dd, *J* = 10.3, 4.5 Hz, 1H), 3.73−3.66 (m, 1H), 3.62 (dd, *J* = 10.3, 5.1 Hz, 1H), 2.13−2.04 (m, 1H), 1.97−1.85 (m, 1H), 1.89 (s, 3H), 1.27 (s, 9H), 1.07 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.9, 150.5, 138.3, 137.1, 135.75, 135.73, 133.30, 133.25, 129.91, 129.87, 128.4, 127.87, 127.85, 127.6, 127.4, 111.2, 72.0, 65.1, 56.0, 45.1, 39.1, 31.2, 26.98, 26.97, 19.3, 12.8 ppm. HRMS calcd for $C_{36}H_{47}N_2O_4SSi$ [M + H^+], 631.3020; found, 631.3037 (1.8 ppm).

44b: R_f = 0.11 (hexanes/EtOAc, 80:20). $[\alpha]^{25}_D$ −16.3 (*c* 1.0, CH_2Cl_2). Formula: $C_{36}H_{46}N_2O_4SSi$. MW: 630.9119 g/mol. IR (neat) ν_{max} 3170, 1680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.65−7.59 (m, 4H), 7.47−7.23 (m, 12H), 6.22 (d, *J* = 7.9 Hz, 1H), 4.38 (s, 2H), 3.77 (dd, *J* = 10.5, 4.8 Hz, 1H), 3.56 (dd, *J* = 10.4, 6.9 Hz, 1H), 3.24−3.16 (m, 1H), 2.19−2.07 (m, 1H), 2.04−1.96 (m, 1H), 1.93 (s, 3H), 1.30 (s, 9H), 1.04 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.2, 150.7, 138.3, 136.9, 135.64, 135.61, 133.2, 133.1, 130.02, 129.96, 128.4, 128.3, 127.91, 127.87, 127.7, 111.8, 72.8, 64.6, 54.7, 45.3, 39.2, 31.1, 26.9, 25.8, 19.2, 12.8 ppm. HRMS calcd for $C_{36}H_{47}N_2O_4SSi$ [M + H^+], 631.3020; found, 631.3043 (2.7 ppm).

*(−)-1-((1R,3S)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(ethylthio)butyl)-5-methylpyrimidine-2,4(1H,3H)-dione and (−)-1-((1S,3S)-3-(Benzyloxy)-4-((tert-butyldiphenylsilyl)oxy)-1-(ethylthio)-butyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**45a** and **45b**).* Following general procedure D, silylated thymine (1.3 mL, 1.2 mmol, 2.0 equiv of a 0.95 M solution in DCM) and I_2 (0.31 g, 1.2 mmol, 2.0 equiv) were added to a solution of **43b** (0.33 g, 0.62 mmol, 1.0 equiv) in anhydrous THF (7.0 mL, 0.10 M). ^1H NMR spectroscopic analysis of the unpurified product indicated the formation of a 1:1 mixture of 1,2-syn and anti diastereomers. Purification by flash chromatography (hexanes/EtOAc, 80:20) provided **45a** and **45b** (0.32 g, 86%) as a colorless oil.

45a: R_f = 0.10 (hexanes/EtOAc, 80:20). $[\alpha]^{25}_D$ −15.3 (*c* 1.0, CH_2Cl_2). Formula: $C_{34}H_{42}N_2O_4SSi$. MW: 602.8588 g/mol. IR (neat) ν_{max} 3180, 1683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.67−7.57 (m, 4H), 7.47−7.27 (m, 12H), 6.12 (d, *J* = 8.2 Hz, 1H), 4.37 (d, *J* = 10.6 Hz, 1H), 4.30 (d, *J* = 10.6 Hz, 1H), 3.77 (dd, *J* = 10.5, 4.7 Hz, 1H), 3.56 (dd, *J* = 10.4, 7.0 Hz, 1H), 3.25−3.15 (m, 1H), 2.59−2.37 (m, 2H), 2.20−2.06 (m, 1H), 2.04−1.93 (m, 1H), 1.91 (s, 3H), 1.24 (t, *J* = 7.4 Hz, 3H), 1.04 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.2, 151.4, 138.0, 136.0, 135.6, 135.5, 133.1, 133.0, 130.0, 129.9, 128.4, 128.3, 127.85, 127.83, 127.8, 112.1, 77.4, 76.3, 72.8, 64.5, 37.4, 26.9, 25.1, 19.2, 14.5, 12.8 ppm. HRMS calcd for $C_{34}H_{43}N_2O_4SSi$ [M + H^+], 603.2707; found, 603.2724 (1.9 ppm).

45b: R_f = 0.13 (hexanes/EtOAc, 80:20). $[\alpha]^{25}_D$ −44.2 (*c* 1.0, CH_2Cl_2). Formula: $C_{34}H_{42}N_2O_4SSi$. MW: 602.8588 g/mol. IR (neat) ν_{max} 3180, 1681 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.70−7.63 (m, 4H), 7.48−7.20 (m, 12H), 6.02 (t, *J* = 7.3 Hz, 1H),

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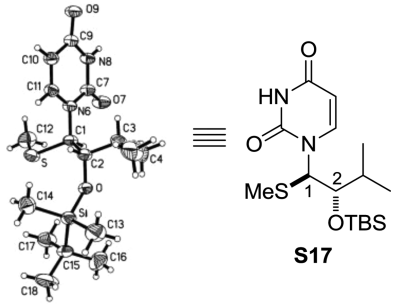
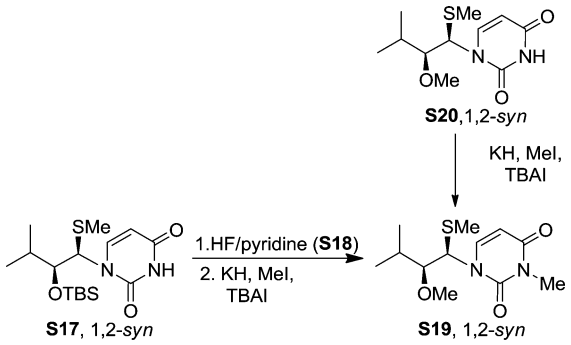
4.58 (d, J = 11.6 Hz, 1H), 4.32 (d, J = 11.5 Hz, 1H), 3.75 (dd, J = 10.1, 4.1 Hz, 1H), 3.70−3.59 (m, 2H), 2.48−2.32 (m, 2H), 2.14−2.03 (m, 1H), 1.97−1.90 (m, 1H), 1.88 (s, 3H), 1.20 (t, J = 7.4 Hz, 3H), 1.07 (s, 9H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.9, 151.2, 138.2, 136.3, 135.70, 135.68, 133.22, 133.19, 129.91, 129.87, 128.4, 127.9, 127.8, 127.71, 127.66, 111.7, 77.3, 72.2, 65.1, 57.1, 37.6, 26.9, 24.9, 19.3, 14.6, 12.7 ppm. HRMS calcd for $C_{34}H_{43}N_2O_4SSi$ [M + H$^+$], 603.2707; found, 603.2732 (3.2 ppm).

Stereochemical Proofs of Structures. The X-ray structure shown below confirms the 1,2-syn stereochemistry with a C2-OTBS (**S17**) and uracil nucleobase.[4]

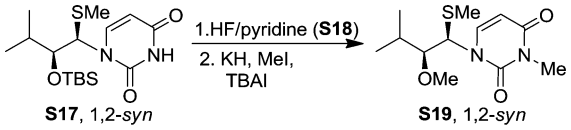


S17

In order to confirm that the 1,2-syn product is also the major diastereomer with a C2-OMe (**S20**),[4] deprotection and methylation from **S17** and methylation of **S20** were performed to ensure formation of the same product **S19**.



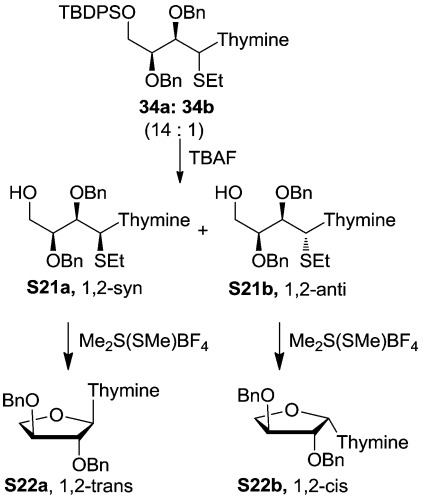
*1-((1R,2S)-2-Methoxy-3-methyl-1-(methylthio)butyl)-3-methylpyrimidine-2,4(1H,3H)-dione (**S19**).*



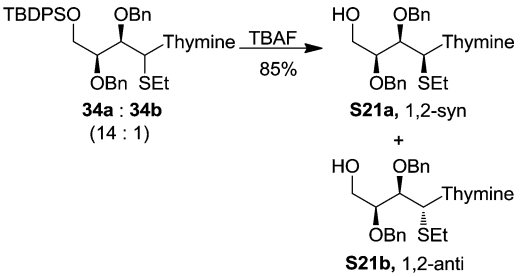
To a solution of **S17**[4] (75 mg, 0.21 mmol, 1.0 equiv) in THF (2.4 mL, 0.09 M) was added HF/pyridine (0.21 mL, 1 mL/mmol). The reaction mixture was stirred at room temperature for 16 h. A saturated solution of $NaHCO_3$ (2 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. To the corresponding alcohol **S18** (55 mg, 0.21 mmol, 1.0 equiv) in a 5:1 mixture of THF/DMF (2.0 mL THF/0.5 mL DMF, 0.08 M) at 0 °C was added KH (19 mg, 0.48 mmol, 2.3 equiv). After stirring for 15 min, MeI (29 μL, 0.48 mmol, 2.3 equiv) and TBAI (18 mg, 0.053 mmol, 0.25 equiv) were added and stirring was continued at room temperature until the reaction was complete based on TLC. A saturated solution of NaCl (2 mL) 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 ($CHCl_3$/MeOH, 96:4) provided **S19** (56 mg, 98%).

S19: R_f = 0.54 ($CHCl_3$/MeOH, 96:4). Formula: $C_{12}H_{20}N_2O_3S$. MW: 272.3638 g/mol. IR (neat) ν_{max} 2996, 1702, 1660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.1 Hz, 1H), 5.85 (d, J = 8.1 Hz, 1H), 5.79 (d, J = 2.8 Hz, 1H), 3.36 (s, 3H), 3.32 (s, 3H), 3.00 (dd, J = 8.6, 2.9 Hz, 1H), 2.01 (s, 3H), 2.00−1.91 (m, 1H), 1.04 (d, J = 2.3 Hz, 3H), 1.02 (d, J = 2.3 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.9, 152.2, 140.0, 101.6, 89.7, 66.7, 61.8, 32.4, 28.1, 19.1, 19.0, 14.2 ppm.

*Deprotection and Cyclization of Thioaminals **34a** and **34b**.*



*(−)-1-((1S,2R,3S)-2,3-Bis(benzyloxy)-1-(ethylthio)-4-hydroxybutyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**S21a**) and 1-((1R,2R,3S)-2,3-Bis(benzyloxy)-1-(ethylthio)-4-hydroxybutyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**S21b**).*

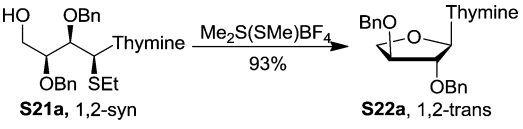


To a solution of **34a**:**34b** (dr 14:1) (0.19 g, 0.26 mmol, 1.0 equiv) in THF (0.50 mL, 0.50 M) was added TBAF (0.39 mL, 0.39 mmol, 1.5 equiv, 1.0 M solution in THF). The reaction mixture was stirred at room temperature for 4 h. A saturated solution of NH_4Cl (1 mL) was added, and the aqueous layer 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 (acetone/DCM, 20:80) provided alcohols **S21a** and **S21b** (0.11 g, 85%).

S21a: R_f = 0.13 (acetone/DCM, 30:70). $[\alpha]^{25}_D$ −159 (c 1.0, CH_2Cl_2). Formula: $C_{25}H_{30}N_2O_5S$. MW: 470.5811 g/mol. IR (neat) ν_{max} 3440, 3184, 1687 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.68 (s, 1H), 7.38−7.27 (m, 8H), 7.24−7.19 (m, 2H), 5.84 (apps, 1H), 4.86 (d, J = 11.3 Hz, 1H), 4.77 (d, J = 11.5 Hz, 1H), 4.69 (d, J = 11.5 Hz, 1H), 4.41 (d, J = 11.4 Hz, 1H), 3.97−3.78 (m, 4H), 2.45 (q, J = 7.4 Hz, 2H), 2.37 (s, 1H), 1.75 (s, 3H), 1.22 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.2, 151.3, 138.4, 138.0, 137.3, 128.52, 128.51, 128.2, 128.1, 128.0, 127.9, 110.3, 82.0, 81.4, 75.4, 73.4, 62.0, 61.6, 25.2, 14.4, 12.5 ppm. HRMS calcd for $C_{25}H_{31}N_2O_5S$ [M + H$^+$], 471.1948; found, 471.1957 (0.7 ppm).

S21b: R_f = 0.21 (acetone/DCM, 30:70). Formula: $C_{25}H_{30}N_2O_5S$. MW: 470.5811 g/mol. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.73 (s, 1H), 7.44−7.27 (m, 10H), 6.03 (d, J = 2.9 Hz, 1H), 4.88 (d, J = 10.9 Hz, 1H), 4.68 (d, J = 10.7 Hz, 1H), 4.64 (s, 2H), 4.05 (dd, J = 7.1, 3.7 Hz, 1H), 3.88−3.71 (m, 2H), 3.50−3.44 (m, 1H), 2.59−2.42 (m, 2H), 2.10 (dd, J = 6.7, 5.6 Hz, 1H), 1.85 (s, 3H), 1.25 (t, J = 7.4 Hz, 3H) ppm. HRMS calcd for $C_{25}H_{31}N_2O_5S$ [M + H$^+$], 471.1948; found, 471.1946 (−1.6 ppm).

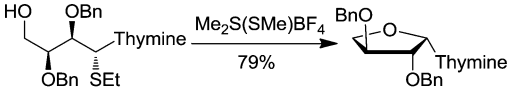
*(+)-1-((2S,3R,4S)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**S22a**).*



dx.doi.org/10.1021/jo502181a | J. Org. Chem. 2014, 79, 10504−10525

To a solution of **S21a** (85 mg, 0.18 mmol, 1.0 equiv) in THF (1.8 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (43 mg, 0.22 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 h. A saturated solution of $NaHCO_3$ (1 mL) 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 (acetone/DCM, 20:80) provided **S22a** (68 mg, 93%) as a white foam: R_f = 0.15 (acetone/DCM, 30:70). $[\alpha]^{25}_D$ +44.0 (*c* 1.0, CH_2Cl_2). Formula: $C_{23}H_{24}N_2O_5$. MW: 408.4471 g/mol. IR (neat) ν_{max} 3181, 1693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.38−7.29 (m, 9H), 7.18−7.14 (m, 2H), 6.05 (s, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 11.3 Hz, 1H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.34 (d, *J* = 10.1 Hz, 1H), 4.19 (dd, *J* = 10.2, 3.5 Hz, 1H), 4.09−4.05 (m, 2H), 1.74 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.4, 150.5, 137.4, 136.8, 136.7, 128.7, 128.6, 128.3, 128.1, 128.0, 127.9, 109.7, 90.1, 85.1, 81.6, 74.2, 72.2, 71.6, 12.5 ppm. HRMS calcd for $C_{23}H_{25}N_2O_5$ [M + H^+], 409.1758; found, 409.1756 (−1.7 ppm).

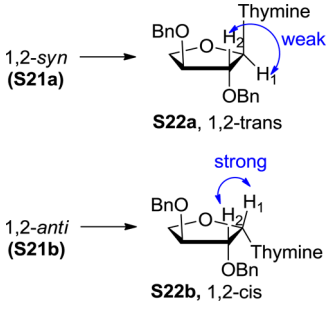
*(−)-1-((2S,3R,4S)-3,4-Bis(benzyloxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**S22b**).*



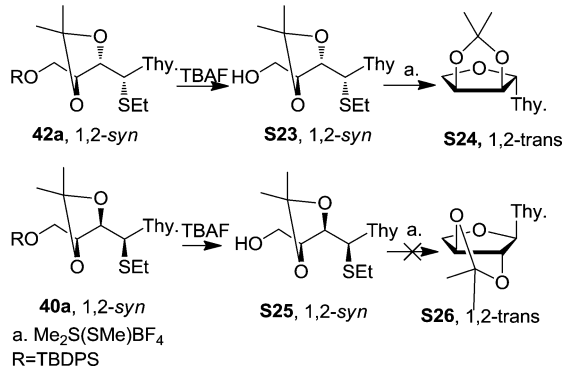
S21b, 1,2-anti **S22b**, 1,2-cis

To a solution of **S21b** (9 mg, 0.019 mmol, 1.0 equiv) in THF (0.2 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (5 mg, 0.023 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 2 h. A saturated solution of $NaHCO_3$ (1 mL) 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 (acetone/DCM, 20:80) provided **S22b** (6.1 mg, 79%): R_f = 0.11 (acetone/DCM, 30:70). $[\alpha]^{25}_D$ −61.0 (*c* 1.0, CH_2Cl_2). Formula: $C_{23}H_{24}N_2O_5$. MW: 408.4471 g/mol. IR (neat) ν_{max} 3203, 1691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.40−7.23 (m, 9H), 7.16−7.11 (m, 2H), 6.20 (d, *J* = 3.8 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.25 (dd, *J* = 9.7, 4.1 Hz, 1H), 4.19 (appd, *J* = 3.8 Hz, 1H), 4.11−4.08 (m, 1H), 4.01 (dd, *J* = 9.8, 1.2 Hz, 1H), 1.89 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.8, 150.2, 137.8, 137.2, 136.8, 128.8, 128.7, 128.4, 128.3, 127.87, 127.86, 109.1, 86.4, 81.3, 80.0, 73.4, 72.0, 71.8, 12.6 ppm. HRMS calcd for $C_{23}H_{25}N_2O_5$ [M + H^+], 409.1758; found, 409.1769 (1.4 ppm).

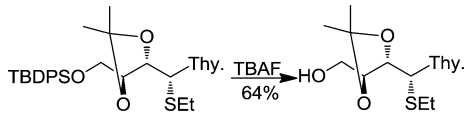
The C1−C2 relative configurations of the synthesized nucleoside analogues were determined by relevant nuclear Overhauser effect (NOE) enhancements (2D NOESY), ^1H NMR coupling constant data, and correlations of chemical shifts. The peaks in the ^1H NMR spectra were assigned using $^1H/^1H$ COSY experiments, chemical shifts, and coupling constants. Proofs of structure for the C1−C2 relative stereochemistry of nucleoside analogues **S22a** and **S22b** were provided by NOESY experiments which are detailed below.



*Deprotection and Cyclization of Thioaminals **42a** and **40a**.*

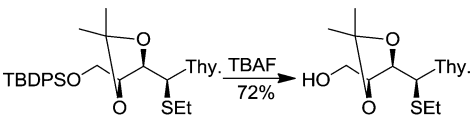


*(±)-1-((R)-(Ethylthio)((4R,5S)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**S23**).*



To a solution of **42a** (0.22 g, 0.39 mmol, 1.0 equiv) in THF (0.80 mL, 0.50 M) was added TBAF (0.58 mL, 0.58 mmol, 1.5 equiv, 1.0 M solution in THF). The reaction mixture was stirred at room temperature for 12 h. A saturated solution of NH_4Cl (1 mL) 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 (hexane/EtOAc, 30:70) provided alcohol **S23** (82 mg, 64%): R_f = 0.19 (hexane/EtOAc, 70:30). Formula: $C_{14}H_{22}N_2O_5S$. MW: 330.3999 g/mol. IR (neat) ν_{max} 3440, 3196, 1693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.71 (s, 1H), 5.98 (d, *J* = 1.5 Hz, 1H), 4.44−4.37 (m, 2H), 4.17−4.10 (m, 1H), 4.07−4.01 (m, 1H), 2.59−2.39 (m, 2H), 1.97 (s, 3H), 1.60 (s, 3H), 1.36 (s, 3H), 1.26 (t, *J* = 7.4 Hz, 3H) ppm. *OH signal missing possibly due to exchange in $CDCl_3$*. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.2, 151.5, 138.0, 111.9, 110.0, 79.7, 77.7, 60.5, 60.2, 26.1, 24.7, 24.6, 14.4, 12.8 ppm. HRMS calcd for $C_{14}H_{23}N_2O_5S$ [M + H^+], 331.1322; found, 331.1336 (2.5 ppm).

*(−)-1-((S)-(Ethylthio)((4R,5S)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**S25**).*



To a solution of **40a** (0.25 g, 0.43 mmol, 1.0 equiv) in THF (0.86 mL, 0.50 M) was added TBAF (0.64 mL, 0.64 mmol, 1.5 equiv, 1.0 M solution in THF). The reaction mixture was stirred at room temperature for 12 h. A saturated solution of NH_4Cl (1 mL) 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 (acetone/DCM, 30:70) provided alcohol **S25** (0.10 g, 72%): R_f = 0.17 (acetone/DCM, 30:70). $[\alpha]^{25}_D$ −122 (*c* 1.0, CH_2Cl_2). Formula: $C_{14}H_{22}N_2O_5S$. MW: 330.3999 g/mol. IR (neat) ν_{max} 3454, 3192, 1692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 5.92 (d, *J* = 1.5 Hz, 1H), 4.25−4.19 (m, 1H), 4.13 (dd, *J* = 8.3, 1.9 Hz, 1H), 3.84 (dd, *J* = 11.9, 4.5 Hz, 1H), 3.76 (dd, *J* = 12.0, 3.8 Hz, 1H), 2.65−2.44 (m, 2H), 1.96 (s, 3H), 1.51 (s, 3H), 1.41 (s, 3H), 1.25 (t, *J* = 7.4 Hz, 3H) ppm. *OH and NH signals missing possibly due to exchange in $CDCl_3$*. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.3, 151.7, 138.0, 111.8, 111.0, 80.9, 79.1, 61.8, 61.6, 27.4, 26.9, 24.9, 14.6, 12.8 ppm. HRMS calcd for $C_{14}H_{22}N_2O_5SNa$ [M + Na^+], 353.1142; found, 353.1135 (−3.4 ppm).

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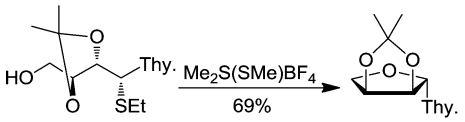
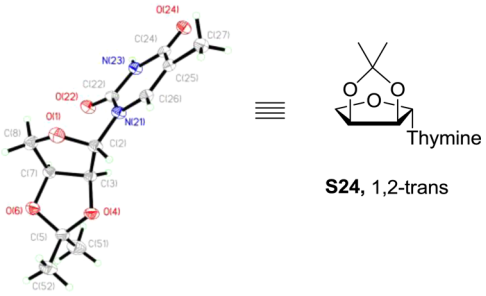
*1-((3aS,4S,6aS)-2,2-Dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**S24**).*



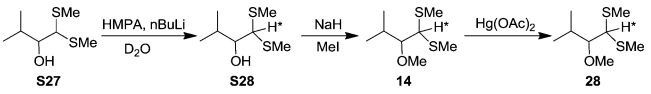
S23, 1,2-*syn* **S24**, 1,2-trans

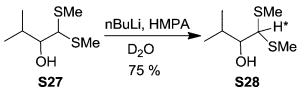
To a solution of **S23** (32 mg, 0.097 mmol, 1.0 equiv) in THF (0.98 mL, 0.10 M) was added $Me_2S(SMe)BF_4$ (28 mg, 0.15 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 2 h. A saturated solution of $NaHCO_3$ (1 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 3 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexane/EtOAc, 30:70) provided **S24** (19 mg, 69%) as a white solid: R_f = 0.33 (hexane/EtOAc, 30:70). Formula: $C_{12}H_{16}N_2O_5$. MW: 268.2658 g/mol. IR (neat) ν_{max} 3207, 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.04 (s, 1H), 5.34 (s, 1H), 5.20 (d, J = 6.1 Hz, 1H), 5.07 (dd, J = 6.0, 4.1 Hz, 1H), 4.36 (dd, J = 9.8, 4.1 Hz, 1H), 4.17 (d, J = 9.8 Hz, 1H), 1.92 (s, 3H), 1.52 (s, 3H), 1.35 (s, 3H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.4, 150.9, 139.9, 112.9, 111.0, 98.5, 85.1, 81.8, 78.0, 26.6, 24.8, 12.5 ppm. HRMS calcd for $C_{12}H_{17}N_2O_5$ [M + H^+], 269.1132; found, 269.1128 (−3.5 ppm).

The stereochemistry of **S24** was confirmed by X-ray analysis.

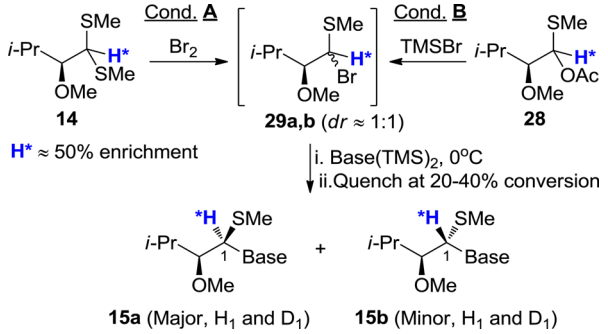


Kinetic Isotope Effects.





*Preparation of ^2H Enriched Dithioacetal **S28**.* To a solution of **S27**[4] (1.8 g, 9.9 mmol, 1.0 equiv) in THF (50 mL, 0.20 M) at −78 °C was added HMPA (17 mL, 99 mmol, 10 equiv) followed by nBuLi (13 mL, 25 mmol, 2.5 equiv of 2.0 M solution in hexanes). The reaction mixture was stirred at −78 °C for 1.5 h. D_2O (1.0 mL, 50 mmol, 5.0 equiv) was added, and the mixture was brought to room temperature. The aqueous layer was extracted with hexanes (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography (hexane/EtOAc, 90:10) provided **S28** (1.35 g, 75%) as a colorless oil that was ∼80% enriched in ^2H.



Measurement of the Kinetic Isotope Effect (KIE) in Table 7. An ∼50% mixture of ^2H enriched substrate **14** or **28** was used to perform

Table 8. Experimental Determination of KIE for the Major 1,2-syn Thioaminal 15a

entry	solvent (conditions)	yield	$1-F$	$\ln(1-F)$	R	R_o	R/R_o	$1-(FR/R_o)$	$\ln[1-(FR/R_o)]$	KIE (k_H/k_D) at 0°C major (**15a**, 1,2-syn)
1	toluene (**B**, TMSBr)	42%	0.58	−0.5447	0.46	0.51	0.9019	0.6212	−0.4761	1.14
					0.45	0.49	0.9184	0.6143	−0.4873	1.12
					0.46	0.50	0.9200	0.6136	−0.4884	1.12
2	toluene (**B**, TMSBr)	39%	0.61	−0.4943	0.48	0.53	0.9057	0.6468	−0.4357	1.13
					0.48	0.52	0.9231	0.64	−0.4463	1.11
					0.46	0.51	0.9019	0.6482	−0.4335	1.14
									average KIE	**1.13 ± 0.01**
3	THF (**A**, Br_2)	22%	0.78	−0.2485	0.46	0.53	0.8679	0.8091	−0.2119	1.17
					0.46	0.54	0.8519	0.8126	−0.2075	1.20
					0.47	0.53	0.8868	0.8049	−0.2170	1.15
4	THF (**A**, Br_2)	7.4%	0.926	−0.0769	0.46	0.54	0.8519	0.9369	−0.0651	1.18
					0.46	0.53	0.8679	0.9358	−0.0664	1.16
					0.44	0.53	0.8302	0.9386	−0.0634	1.21
									average KIE	**1.18 ± 0.02**
5	THF (**B**, TMSBr)	24%	0.76	−0.2744	0.49	0.58	0.8448	0.7972	−0.2266	1.21
					0.49	0.57	0.8597	0.7937	−0.2311	1.19
					0.49	0.59	0.8305	0.8007	−0.2223	1.23
									average KIE	**1.21 ± 0.02**
6	MeCN (**A**, Br_2)	34%	0.66	−0.4155	0.47	0.53	0.8868	0.6985	−0.3588	1.16
					0.48	0.52	0.9231	0.6862	−0.3767	1.10
					0.44	0.51	0.8627	0.7067	−0.3472	1.20
7	MeCN (**A**, Br_2)	10%	0.90	−0.1054	0.46	0.53	0.8679	0.9132	−0.0908	1.16
					0.45	0.52	0.8654	0.9135	−0.0905	1.16
					0.46	0.51	0.9019	0.9098	−0.0945	1.12
									average KIE	**1.15 ± 0.04**

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Table 9. Experimental Determination of KIE for the Minor 1,2-anti Thioaminal 15b

										KIE (k_H/k_D) at 0°C
entry	solvent (conditions)	yield	$1-F$	$\ln(1-F)$	R	R_o	R/R_o	$1-(FR/R_o)$	$\ln[1-(FR/R_o)]$	minor (**15b**, 1,2-anti)
1	toluene (**B**, TMSBr)	42%	0.58	−0.544	0.51	0.51	1.0	0.58	−0.5447	1.0
					0.52	0.49	1.0612	0.5543	−0.5901	0.92
					0.51	0.50	1.02	0.5716	−0.5593	0.97
2	toluene (**B**, TMSBr)	39%	0.61	−0.4943	0.52	0.53	0.9811	0.6174	−0.4823	1.03
					0.52	0.52	1.0	0.61	−0.4943	1.0
					0.50	0.51	0.9804	0.6176	−0.4818	1.03
									average KIE	**0.99 ± 0.04**
3	THF (**A**, Br_2)	22%	0.78	−0.2485	0.55	0.53	1.0377	0.7717	−0.2592	0.96
					0.57	0.54	1.0556	0.7678	−0.2643	0.94
					0.57	0.53	1.0755	0.7634	−0.2699	0.92
4	THF (**A**, Br_2)	7.4%	0.926	−0.0769	0.59	0.54	1.0926	0.9192	−0.0843	0.91
					0.58	0.53	1.0943	0.9190	−0.0845	0.91
					0.60	0.53	1.1321	0.9162	−0.0875	0.88
									average KIE	**0.92 ± 0.03**
5	THF (**B**, TMSBr)	24%	0.76	−0.2744	0.57	0.58	0.9828	0.7641	−0.2691	1.02
					0.57	0.57	1.0	0.76	−0.2744	1.0
					0.56	0.59	0.9492	0.7722	−0.2585	1.06
									average KIE	**1.03 ± 0.03**

the KIE study. The ^{1}H NMR of the starting mixture was taken prior to the reaction (d_1 relaxation delay 10 s). Complete conversion to the bromothioether intermediates **29a,b** was confirmed by ^{1}H NMR. The reactions were quenched after 10−40% conversion, as judged by disappearance of the H1 signal of **29**, and by the yield obtained for **15a,b** after purification of the crude mixtures. Incorporation of ^{2}H into thioaminals **15a** and **15b** was determined using the ^{1}H NMR spectra of the pure mixtures. Each spectrum was integrated at least three times, and the values were recorded in the following tables. The kinetic isotope effects were determined using the following equation:[41,56] $\mathrm{KIE} = \ln(1-F)/\ln(1-F(R/R_o))$, where F is the fractional conversion of the starting material (yield of **15a,b**) and R and R_o are the ratios of the H2 or OMe and anomeric (H1) resonances in the products **15** (R) and in the bromothioether **29a,b** (R_o).

Conditions A. To a solution of ^{2}H enriched **14** in anhydrous solvent (0.10 M) was added Br_2 (1.1 equiv) at −40 °C, and the resulting mixture was stirred for 10 min (the activation occurred much faster in MeCN; therefore, the mixture was only stirred for 30 s). Silylated thymine (1.4 equiv) was then added, and the reaction was warmed to 0 °C. The reaction was quenched with a saturated solution of $Na_2S_2O_3$ after 1 h at 0 °C in THF or 15 min in MeCN.

Conditions B. To a solution of ^{2}H enriched **28** in deteurated anhydrous solvent (0.10 M) was added TMSBr (1.5 equiv) at 0 °C (20 min.). Silylated thymine (1.4 equiv) was added, and the reaction was maintained at 0 °C for ∼1 h after which a saturated solution of $NaHCO_3$ was added. The standard deviation was calculated from the following equation:

$$\sqrt{\frac{\sum_{i=1}^{n}(x_i-\bar{x})^2}{(n-1)}}$$

where n denotes the number of spectra, x_i denotes the KIE calculated for each spectrum, and $\bar{x}$ denotes the average of all KIE.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR and ^{13}C NMR spectra are available for all new compounds. Details concerning the computational method, energies, and Cartesian coordinates for all the transition structures and intermediate geometries are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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