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Organocatalytic Conversion of Nucleosides to Furanoid Glycals

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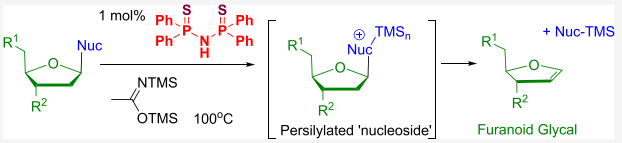
ABSTRACT: A class of organocatalysts that are highly active for the conversion of 2′-deoxynucleosides to furanoid glycals have been discovered. These phosphorimides, $(Ph_2PS)_2NH$ and $(Ph_2PSe)_2NH$, were shown to effectively mediate persilylation of 2′-deoxynucleosides allowing the elimination of the nucleobase giving the corresponding glycal. These mild conditions were demonstrated in the syntheses of glycals with various substitution patterns while minimizing the formation of undesired byproducts and expanding the scope of this methodology.



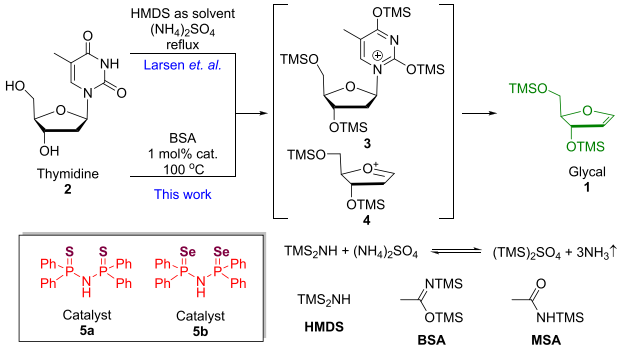
INTRODUCTION

Furanoid glycals are key intermediates in the syntheses of nucleosides, carbohydrates, and their derivatives, which are commonly investigated for antiviral, anticancer, and antibacterial properties.[1] In addition, furanoid glycals are easily accessible sources of defined stereocenters, making them good chiral building blocks for the synthesis of natural products and biological molecules.[2] As such, there has been considerable effort toward the development of methods for forming these glycals.[2] Previously reported methods involve the installation of the double bond of the glycal from a ribose or deoxyribose derivative, through a base-mediated elimination of a leaving group[3] or activation and subsequent reductive elimination of the 2 and 3 substituents.[4] The molybdenum-catalyzed intramolecular cyclo-isomerization of alkynols prepared via multistep routes was also reported to form furanoid glycals.[5] Many of these methods require undesirably harsh reaction conditions and reagents such as those used in dissolving metal reductions (lithium, sodium, or zinc), toxic reagents (selenium compounds for oxidation/elimination), and involve cumbersome multistep syntheses to arrive at the appropriate precursor (such as the phenylselenyltetrahydrofurans, the alkynols for the Mo-catalyzed cyclizations, and the furanosyl halides for reductive eliminations) for the glycal-forming step.

RESULTS AND DISCUSSION

The simplest preparation of furanoid glycals in the literature to the best of our knowledge is a one-step reaction starting with inexpensive (<$1/g), commercially available thymidine (Scheme 1) by Pedersen et al.[6] The reaction, using HMDS and ammonium sulfate, presumably involves formation of the powerful silylating agent bistrimethylsilyl sulfate from the reaction of HMDS with ammonium sulfate followed by *in situ* per-silylation of thymidine, resulting in the relatively quick elimination of the nucleobase to form the glycal. However, this method involved high temperatures, a large excess of HMDS used as a solvent, and variable yields attributed to the formation of undesired polymeric byproducts. In addition, there was a necessity to remove ammonia gas, which was evolved over the course of the reaction since the reaction between HMDS and ammonium sulfate is reversible. Failure to remove the gas resulted in hindrance of the reaction and decomposition, which posed a significant concern on a larger scale. In addition, the aqueous workup can also result in the undesired hydrolysis of the trimethylsilyl protecting groups, especially with the extended operation time typically required on a larger scale. Despite these shortcomings, we were attracted to the simplicity and cost-effectiveness of this approach. We sought to find reaction conditions for the silylation and elimination of thymidine to form furanoid glycals, which were milder, higher yielding, and reliable.

Scheme 1. One-Step Eliminations to Form Furanoid Glycals



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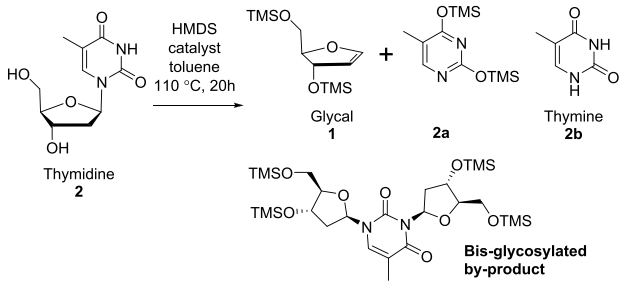
With the aforementioned goals in mind, an extensive screen of catalysts was undertaken; selected results are shown (Table 1). Initially, $(PhSO_2)_2NH$ showed promising results achieving high conversion with only a 1 mol % catalyst, but the assay yield was <80% due to the formation of a bis-glycosylated impurity,[7] necessitating vacuum distillation for isolation of pure **1**. After further screening, we found the thio-derivatives to be more active catalysts than the oxy-derivatives (entries 4−6, Table 1), likely due to the better silylating ability of the TMS-thio analogues. A further boost in catalytic activity was observed going from the thio- to the seleno-derivatives (entries 7 and 8, Table 1). The dithiophosphorimide **5a** (X = S, entry 8, Table 1) was identified as a highly active silyl transfer catalyst, which was effective for the formation of glycals as low as 0.5 mol %. The diselenophosphorimide **5b** (X = Se, entry 8, Table 1) was even more active giving full conversion even with a 0.05 mol % catalyst. The assay yields of glycal **1** from thymidine using **5a** or **5b** were >98%. To the best of our knowledge, these organocatalysts have not been previously reported to demonstrate any activity in silylations. Instead, they have primarily been used as ligands for inorganic and organometallic chemistry.[8]

Additionally, since effectively eliminating ammonia generated from HMDS was challenging, an alternative silylating agent was desired. We identified *N,O*-bis(trimethylsilyl)-acetamide (BSA) as a suitable silylating agent, which did not raise such issues upon reaction scale-up. Although the catalyst can mediate the transfer of the remaining trimethylsilyl group from *N*-(trimethylsilyl)acetamide (MSA), the transfer of the trimethylsilyl group from MSA is much slower requiring extended heating, leading to decomposition. Thus, 1 equiv of BSA per required silyl group transfer was used (2 equiv for silylation to form bis-TMS-thymine **2a** and 1 equiv of BSA for silylation of each alcohol present in the nucleoside starting material). The use of the more reactive and expensive *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) did not allow the reduction of silylating agents required for reaction completion.

The addition of 2,6-lutidine or 2,4,6-collidine minimized the acid-catalyzed elimination of **1** to the furan (Scheme 2) by neutralization of trace adventitious acid. As a result, rapid conversion with a virtually quantitative yield, independent of the reaction scale, was observed for the formation of the bis-trimethylsilyl glycal **1** from thymidine on a >100 g scale. Glycal **1** was found to be unstable to storage unless a base is added to suppress the facile elimination to the furan. An array of commercially available deoxynucleosides was also subjected to the optimized reaction conditions to further demonstrate the scope of this method (Table 2).

Table 1. Selected Results from the Catalyst Screen[a]



Entry	Catalyst	X=O		X=S		X=Se	
		mol%	conv[b]	mol%	conv[b]	mol%	conv[b]
1	$(NH_4)_2SO_4$	20	98[c]	-	-	-	-
2	H_2SO_4	20	99[c]	-	-	-	-
3	$(PhSO_2)_2NH$	1	98[e]	-	-	-	-
4	Saccharin[d]	3	21[d]	0.6	83[e]	-	-
5	C_6F_5XH[g]	20	0	20	59[e]	-	-
6	$PhCXNH_2$[g]	20	0	20	39[f]	-	-
7	NH_2CXNH_2[g]	15	0	11	26[e]	2.5	60[e]
8	$(Ph_2PX)_2NH$[g]	5	2	0.5	**99.5**	0.05	**>99.9**

[a]Reaction conditions: 4.0 equiv of HMDS in 10 vol toluene at reflux. [b]Conversion by HPLC area % (210 nm) monitoring conversion of thymidine to thymine (after sample hydrolysis). [c]Reaction mixture discoloration was observed with the formation of varying amounts (20−40%) of polymeric byproducts. [d]X refers to the carbonyl on the saccharin. [e]15−25% formation of a bis-glycosylated byproduct was observed. [f]50% formation of a bis-glycosylated byproduct was observed. [g]Entry 5: pentafluorophenol (X = O), pentafluorothiophenol (X = S); entry 6: benzamide (X = O), thiobenzamide (X = S), selenobenzamide (X = Se); entry 7: urea (X = O), thiourea (X = S), selenourea (X = Se); entry 8: $[Ph_2PO]_2NH$ (X = O), $[Ph_2PS]_2NH$ **5a** (X = S), $[Ph_2PSe]_2NH$ **5b** (X = Se).

Scheme 2. Decomposition of Glycal

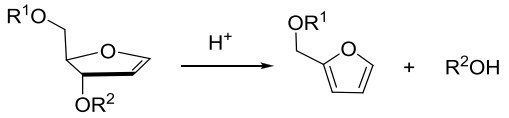
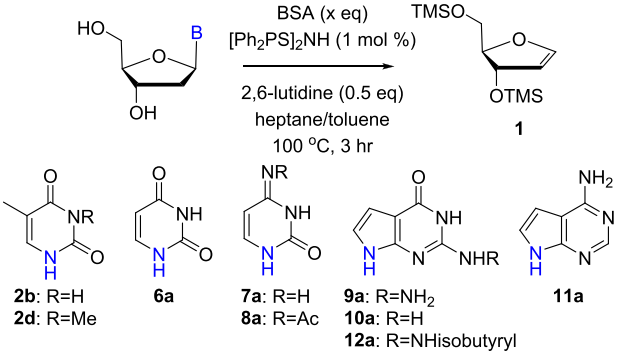


Table 2. Formation of Bis-TMS Glycal from Deoxynucleosides



entry	nucleoside (2′-deoxy)	nucleobase	BSA (equiv)	assay % yield[a]
1	thymidine **2**	**2b**	4.5	>98
2	deoxyuridine **6**	**6a**	4.5	87
3	deoxycytidine **7**	**7a**	4.5	97
4	N^4-acetyldeoxycytidine **8**	**8a**	3.5	74
5[b]	deoxyguanosine **9**	**9a**	10	82
6	deoxyinosine **10**	**10a**	3.5	85
7	deoxyadenosine **11**	**11a**	4.5	0
8	N^2-isobutyryldeoxyguanosine **12**	**12a**	5.5	0
9	3-methylthymidine **2c**	**2d**	4.5	0

[a]Assay yield determined by quantitative ^{1}H NMR of the crude reaction mixture, glycal peaks integrated against the internal standard (2,6-lutidine). All reactions reached >99% conversion. [b]Commercially available deoxyguanosine is a hydrate with variable amounts of moisture; thus, use of 5 equiv of BSA resulted in low conversion.

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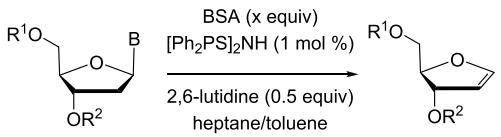
To our delight, pyrimidine-based deoxynucleosides **2**, **6**, **7**, and **8** reacted smoothly to give the glycal **1** in 87−98% yields. Previously, Pedersen et al.'s reported method[6] did not result in glycal formation from purine nucleosides. In agreement with the literature, 2′-deoxyadenosine **11** did not yield any glycal. Interestingly, under these reaction conditions, purine nucleosides deoxyguanosine **9** and deoxyinosine **10** smoothly produced glycal. In contrast, the N^2-protected deoxyguanosine **12** and the *N*-methylated thymidine **2c** did not result in any observable conversion. While the nucleobases on **11**, **12**, and **2b** are potentially able to be silylated to generate the positively charged ion, this alone is not enough to affect the elimination, indicating the dependence on the ease of the persilylated cationic nucleoside intermediate for the elimination to proceed.

Despite the labile TMS groups, **1** can withstand the aqueous workup at smaller scales. However, some desilylation as well as decomposition of the glycal to the furan side product inevitably occurs (Scheme 2), especially after silica gel chromatography. The loss of the TMS groups from **1** during aqueous workup can be avoided by the addition of *i*PrOH, which in the presence of catalyst **5a** desilylates MSA forming the volatile *i*PrOTMS and acetamide, which can simply be removed by filtration after dilution with hexane. Then, evaporation afforded the pure glycal without chromatographic purification.

Next, we examined the reactivity of nucleosides differentially protected on the ribose (Table 3). All the protected nucleosides were either commercially available or readily synthesized from commercial materials. Reactions with 5′ and 3′ silyl-protected thymidines proceeded smoothly, giving full conversion in less than 3 h. In general, TBDPS-protected glycals gave higher yields than their TBDMS-protected counterparts, perhaps owing to the differences in the robustness of the protecting groups. The cyclic 1,1,3,3-tetraisopropyl-1,3-disiloxanediyl (TIPDS)-protected deoxyuridine **18** was also eliminated to give the protected glycal in 70% yield, although the reaction was considerably slower than other substrates, requiring 24 h for full conversion, potentially due to ring strain in the glycal. Trityl-protected glycals, which have not been previously synthesized in this fashion, also produced products, although glycal **19a** was obtained in a much lower yield than glycal **20a** due to the instability of the trimethylsilyl group. Thus, a variety of protected glycals can be synthesized from easily accessible precursors. In accordance with a previous report of this reaction using HMDS and ammonium sulfate,[6] thymidine **21** bearing a 3′-ester group did not successfully convert to glycal even under our basic reaction conditions; instead, crude NMR shows the full conversion of the starting material into its furfuryl alcohol derivative (Scheme 2).

Table 3. Differentially Protected Glycals



entry	deoxynucleoside/ glycal	R^1	R^{2a}	BSA (equiv)	isolated % yield
1	**13**/**13a**	TBDMS	H/TMS	3.5	63
2	**14**/**14a**	TBDMS	TBDMS	2.5	93
3	**15**/**15a**	TBDPS	H/TMS	3.5	91
4	**16**/**16a**	TBDPS	TBDPS	2.5	89
5	**17**/**17a**	TBDPS	TBDMS	2.5	89
6[b]	**18**/**18a**	TIPDS	TIPDS	2.5	70
7	**19**/**19a**	trityl	H/TMS	3.5	53
8	**20**/**20a**	trityl	TBDMS	2.5	85
9	**21**/**21a**	trityl	Piv	3.5	0, (82)[c]

[a]Deoxynucleoside starting material with an unprotected hydroxyl group is trimethylsilylated over the course of the reaction. The silyl groups are retained during workup of the glycal. [b]Reaction complete after 24 h. [c]No glycal product was observed, even with 1 equiv of triethylamine added to the reaction as a base to prevent elimination to the furan; 82% of tritylfurfuryl ether was isolated.

Subsequently, we explored a few differentially substituted nucleosides (Table 4). 5′-Silylated 2′,3′-dideoxythymidine **22** gave the corresponding 3′-deoxyglycal in excellent yield. The glycal was also much more stable than its 3′-hydroxy counterparts, and no decomposition to furfuryl alcohol was observed even upon extended storage at room temperature due to the lack of the leaving group at the 3′ position. 3′-Azido thymidine (AZT) **23** did not give any glycal product due to elimination to form the furan. In contrast to deoxynucleosides **21** and **23**, the 3′-Boc-protected amine **24** readily formed the glycal in a modest 73% yield, and the minimal elimination product was observed throughout the reaction and upon workup. 5′*O*-Tritylated deoxythymidine in the *xylo* configuration (**25**) formed the product also, resulting in a glycal with a 5′,3′-*syn* configuration. The 2′-α and -β fluoro uridines **26** and **27** resulted in no conversion under the reaction conditions. In theory, the electron-withdrawing fluoro substituent should lower the pK_a of the 2′-proton, enhancing reactivity. However, the substitution of the 2′-position from a hydrogen to a fluorine enhances the stability of the *N*-glycosidic bond,[9] and this effect seems to dominate. Similarly, the *N*-glycosidic bond is also stronger in a ribonucleoside than a deoxynucleoside. Accordingly, ribo-thymidines **28** and **29** both failed to give any conversion. In contrast, a methyl substituent on the 2′-position allowed the reaction to proceed. A 2:1 mixture of diastereomers of **30** was subjected to the reaction, giving glycal **30a** in a modest 70% yield due to decomposition of **30a** during the workup forming the furan. The major (alpha/beta) methyl isomer was consumed more rapidly than the minor diastereomer likely due to steric effects; full conversion to glycal was seen after 24 h. This indicates that the mechanism likely involves simple E2 elimination of the positively charged bis-silylated nucleobase or proceeds via an oxonium ion intermediate where either of the 2′-protons can be abstracted to give the glycal.

Early mechanistic studies were conducted to better understand the reactivity of the dithiophosphorimide catalyst (Figure 1). The energies of the silylated versions of $[Ph_2PS]_2NH$ and its phosphine oxide equivalent $[Ph_2PO]_2NH$ were compared. It was found that the Si−S bond is weaker than the Si−O bond, such that the thiophosphorimide was preferentially silylated at the *N*-position, while the oxo derivative prefers to be silylated at the oxygen. Additionally, the DFT-computed energetics of proton transfer between $[Ph_2PO]_2NH$ and **5a** predicted **5a** to be more acidic by 3.8 pK_a units in toluene, making **5a** a superior leaving group during the silyl transfer reaction (see the Supporting Information). Furthermore, the diselenophosphorimide **5b** was predicted to be more acidic than **5a** by 1.7 pK_a units, suggesting that the selenium derivative should be even more active than the sulfur-based

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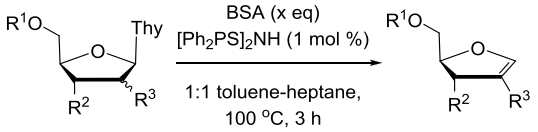
Table 4. Differentially Substituted Nucleosides



entry	nucleoside/glycal	R^1	R^2	R^3	BSA (equiv)	isolated % yield[a]
1	**22**/**22a**	TBDPS	H	H	2.5	92[a]
2	**23**/**23a**	H	N_3	H	3.5	0, (83)[f]
3	**24**/**24a**	H/TMS	NHBoc	H	4.5	73[a]
4	**25**/**25a**	trit	β-OH	H	3.5	83[a]
5[c]	**26**/**26a**	H	β-OH	β-F	3.5	0[b]
6[c]	**27**/**27a**	H	β-OH	α-F	3.5	0[b]
7	**28**/**28a**	H	β-OH	β-OH	5.5	0[b]
8	**29**/**29a**	H	α-OH	α-OH	5.5	0[b]
9[c]	**30**/**30a**[e]	TIPDS	OTIPDS	Me[d]	2.5	70[a]

[a]Isolated yield. [b]Assay yield (HPLC, NMR) after 24−48 h. [c]Nucleobase was uracil. [d]3:1 mixture of diastereomers. [e]Reaction complete after 24 h. [f]No glycal product was observed, even with 1 equiv of triethylamine added to the reaction mixture as a base to prevent elimination to the furan; 83% of furfuryl alcohol was isolated as its TMS ether.

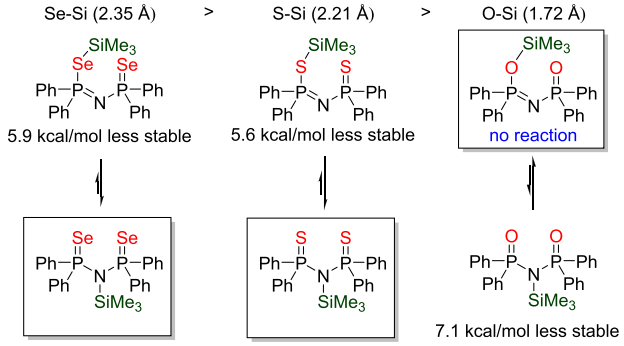


Figure 1. Energy calculations for the organocatalyst and related derivatives.

catalyst, which was confirmed experimentally also, effectively catalyzing the reaction at 0.05 mol %. Preliminary experiments also revealed that the dithiophosphorimide catalyst is able to catalyze the trimethylsilylation of hindered secondary and tertiary alcohols in the presence of BSA or HMDS under mild conditions and will be reported in due course.

CONCLUSIONS

In summary, we report an updated method on the silylation-elimination reaction of deoxynucleosides to form furanoid glycals. This reaction is mediated by a highly effective organocatalyst with unprecedented silyl transfer activity. The developed conditions are mild and scalable, allowing access to large quantities of a variety of protected and differentially substituted glycals, which are highly useful precursors for the syntheses of nucleosides and other biomolecules. The preparation of several unnatural nucleosides using these glycals will be reported in due course. Since the new conditions require a minimal amount of catalyst and produce virtually pure products, the unstable glycals can often be used without further purification.

EXPERIMENTAL SECTION

General Information. Solvents and reagents were purchased from commercial sources and used as received. Nucleosides **2**, **6**, **7**, **8**, **9**, **10**, **11**, **18**, **19**, **23**, **25**, **26**, **27**, **28**, and **29** were purchased from commercial sources (Combi-Blocks, Alfa Aesar, Acros Organics, Chem Impex International, Sigma-Aldrich, Carbosynth, Angene, AK Scientific, Activate Scientific). Organocatalysts **5a** and **5b**[10] and nucleosides **13**,[6b] **14**,[6b] **15**,[6b] **16**,[6b] **17**,[6b] **20**,[11] and **24**[12] were synthesized according to literature procedures. Glycals **1**,[6a] **13a**,[13] **14a**,[6b] **15a**,[6a] **16a**,[6b] **17a**,[6b] **18a**,[14] and **22a**[15] are known in the literature and were compared to reported data. Infrared spectra were recorded on a Nicolet 6700 FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded on a Bruker 400, 500, or 600 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) referenced to the residual solvent resonance ($CDCl_3$: δ 7.24, CD_2Cl_2: δ 5.32). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Bruker 101 or 126 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal reference ($CDCl_3$: δ 77.0, CD_2Cl_2: δ 53.84, CD_3CN: δ 1.93). Chromatography was performed using a Teledyne ISCO Combiflash Rf 200i with RediSep Rf Gold-prepacked silica gel columns. HRMS data was obtained on a Bruker Solarix FT-ICR MS. All samples were introduced to the system via direct infusion (infusion rate 180 μL/h) and analyzed under ESI positive mode.

General Procedure for the Formation of Bis-TMS-Glycal 1 for the Catalyst Screen. In an 8 mL vial, deoxynucleoside (1 mmol), catalyst (0.01 equiv, 5 mg), 2,6-lutidine (0.5 equiv, 58 μL), 1 mL of heptane, 1 mL of toluene, and the specified amount of BSA were added under a nitrogen atmosphere. The reaction was stirred at 100 °C for 3 h. Reaction progress was monitored via HPLC by the presence of the starting material. NMR of the crude reaction mixture was taken in deuterated methylene chloride, and the internal standard (2,6-lutidine) was used to determine the assay yield.

*Trimethyl(((2R,3S)-3-((trimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)-methoxy)silane (**1**).* ^1H NMR (400 MHz, CD_2Cl_2) δ 6.52 (d, J = 2.7 Hz, 1H), 5.08 (t, J = 2.6 Hz, 1H), 4.87 (t, J = 2.5 Hz, 1H), 4.32 (td, J = 6.4, 2.6 Hz, 1H), 3.60 (ddd, J = 83.6, 10.6, 6.4 Hz, 2H), 0.20 (s, 9H), 0.19 (s, 9H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 149.5, 104.0, 89.3, 76.3, 62.7, −0.3, −0.5.

General Procedure for Synthesis of Glycals. In an 8 mL vial, deoxynucleoside (1 mmol), catalyst (0.01 equiv, 5 mg), 2,6-lutidine (0.5 equiv, 58 μL), 1 mL of heptane, 1 mL of toluene, and the specified amount of BSA were added under a nitrogen atmosphere. The reaction was stirred at 100 °C until completion. Reaction progress was monitored via HPLC and NMR of the crude mixture by the presence of the starting material. After the starting material was completely consumed, the reaction mixture was extracted with methylene chloride and water. The organic layer was washed four to five times with water and once with brine and then dried over

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anhydrous sodium sulfate. The organic phase was passed through a plug of neutral alumina and washed with two volumes of heptane. The filtrate was concentrated *in vacuo* to give the product. (Glycal products not bearing TMS ethers can also be purified by column chromatography.) The crude reaction mixture was directly injected onto a prepacked column and eluted with hexanes with 1% triethylamine.

*tert-Butyldimethyl(((2R,3S)-3-((trimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)silane (**13a**).* **13a** was prepared according to the general procedure from **13** (1 mmol, 356 mg) to yield a colorless oil (190 mg, 63%). FT-IR (ATR, neat): 1610, 1485, 1440, 1260, 1080 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ 6.47 (d, J = 2.6 Hz, 1H), 5.02 (t, J = 2.6 Hz, 1H), 4.84 (t, J = 2.5 Hz, 1H), 4.25 (td, J = 6.1, 2.6 Hz, 1H), 3.68 (dd, J = 10.6, 5.7 Hz, 1H), 3.49 (dd, J = 10.6, 6.5 Hz, 1H), 0.90 (s, 9H), 0.13 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 149.5, 103.9, 89.4, 76.1, 63.3, 26.2, 18.1, 0.6, −5.10, −5.13.

*tert-Butyl(((2R,3S)-3-((tert-butyldimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)dimethylsilane (**14a**).* **14a** was prepared according to the general procedure from **14** (1 mmol, 471 mg) to yield a colorless oil (320 mg, 93%). FT-IR (ATR, neat): 1615, 1475, 1465, 1250, 1080 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ 6.47 (dd, J = 2.6, 0.8 Hz, 1H), 5.01 (t, J = 2.6 Hz, 1H), 4.87 (td, J = 2.6, 0.8 Hz, 1H), 4.29 (td, J = 6.0, 2.8 Hz, 1H), 3.69 (dd, J = 10.7, 5.7 Hz, 1H), 3.51 (dd, J = 10.7, 6.3 Hz, 1H), 0.90 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 149.1, 103.6, 89.1, 76.1, 63.0, 26.1, 26.0, 18.5, 18.2, −4.1, −4.3, −5.2, −5.2.

*tert-Butyldiphenyl(((2R,3S)-3-((trimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)silane (**15a**).* **15a** was prepared according to the general procedure from **15** (1 mmol, 481 mg) to yield a colorless oil (390 mg, 91%). FT-IR (ATR, neat): 1610, 1430, 1250, 1080 cm^{-1}. ^1H NMR (500 MHz, CD_3CN) δ 7.70 (m, 4H), 7.51−7.37 (m, 6H), 6.54 (d, J = 2.6 Hz, 1H), 5.08 (t, J = 2.6 Hz, 1H), 4.95 (m, 1H), 4.30 (td, J = 5.5, 2.8 Hz, 1H), 3.73 (dd, J = 11.0, 5.6 Hz, 1H), 3.67 (dd, J = 11.0, 5.3 Hz, 1H), 1.08 (s, 9H), 0.14 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3CN) δ 149.0, 135.5, 133.3, 133.3, 129.9, 127.8, 117.3, 103.7, 88.8, 75.4, 63.7, 26.2, 18.9, −0.6.

*tert-Butyl(((2R,3S)-3-((tert-butyldiphenylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)diphenylsilane (**16a**).* **6a** was prepared according to the general procedure from **16** (1 mmol, 705 mg) to yield a yellow oil (530 mg, 89%). FT-IR (ATR, neat): 1610, 1430, 1110, 1080 cm^{-1}. ^1H NMR (500 MHz, CD_3CN) δ 7.66−7.62 (m, 4H), 7.55−7.51 (m, 4H), 7.45−7.32 (m, 12H), 6.51 (d, J = 2.2 Hz, 1H), 4.94 (dt, J = 2.8, 0.9 Hz, 1H), 4.91 (t, J = 2.6 Hz, 1H), 4.42 (ddd, J = 5.7, 4.3, 2.9 Hz, 1H), 3.42 (dd, J = 11.1, 4.0 Hz, 1H), 3.36 (dd, J = 11.1, 4.0 Hz, 1H), 1.01 (s, 9H), 0.90 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_3CN) δ 150.5, 136.7, 136.6, 136.4, 136.4, 134.8, 134.7, 134.2, 134.2, 130.9, 130.9, 130.8, 128.8, 128.7, 128.7, 118.3, 104.3, 89.9, 77.9, 64.8, 27.3, 27.1, 19.7, 19.5.

*tert-Butyldiphenyl(((2R,3S)-3-((trimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)silane (**17a**).* **17a** was prepared according to the general procedure from **17** (1 mmol, 595 mg) to yield a colorless oil (416 mg, 89%). FT-IR (ATR, neat): 1610, 1475, 1465, 1430, 1250, 1080 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.79−7.08 (m, 10H), 6.48 (d, J = 2.5 Hz, 1H), 5.04 (t, J = 2.6 Hz, 1H), 4.94 (t, J = 2.3 Hz, 1H), 4.32 (td, J = 5.4, 2.9 Hz, 1H), 3.71 (dd, J = 10.9, 5.6 Hz, 1H), 3.64 (dd, J = 10.9, 5.3 Hz, 1H), 1.05 (s, 9H), 0.88 (s, 9H), 0.07 (s, 6H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 149.6, 136.2, 134.0, 130.3, 128.3, 104.2, 89.7, 76.6, 64.4, 27.1, 26.2, 19.7, 18.5, −4.0, −4.2.

*1,4-Anhydro-2-deoxy-3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-D-erythro-pent-1-entiol (**18a**).* **18a** was prepared according to the general procedure from **18** (1 mmol, 471 mg) to yield a yellow oil (250 mg, 70%). FT-IR (ATR, neat): 1620, 1470, 1385, 1250, 1085 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) δ 6.43 (dd, J = 2.6, 1.4 Hz, 1H), 5.27 (ddd, J = 4.1, 2.4, 1.5 Hz, 1H), 5.06 (t, J = 2.6 Hz, 1H), 4.37 (dt, J = 11.3, 4.5 Hz, 1H), 4.13 (dd, J = 11.0, 4.6 Hz, 1H), 3.59 (t, J = 11.2 Hz, 1H), 1.27−0.83 (m, 28H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2) δ 148.8, 103.3, 89.0, 78.4, 64.6, 18.0, 17.8, 17.8, 17.6, 17.5, 17.4, 17.3, 17.2, 14.2, 13.8, 13.5, 13.1.

*Trimethyl(((2R,3S)-2-((trityloxy)methyl)-2,3-dihydrofuran-3-yl)oxy)silane (**19a**).* **19a** was prepared according to the general procedure from **19** (1 mmol, 471 mg) to yield a pale yellow oil (230 mg, 53%). FT-IR (ATR, neat): 1610, 1495, 1450, 1250, 1075 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.66−7.17 (m, 15H), 6.55 (d, J = 2.5 Hz, 1H), 5.05 (t, J = 2.6 Hz, 1H), 4.83 (t, J = 2.4 Hz, 1H), 4.34 (td, J = 5.2, 3.0 Hz, 1H), 3.15 (d, J = 5.3 Hz, 2H), 0.07 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 149.7, 144.5, 129.2, 128.5, 128.4, 127.7, 127.6, 104.2, 88.4, 76.6, 64.3, 0.6. HRMS (ESI/FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{27}H_{30}NaO_3Si^+$ 453.1856; found 453.1854.

*tert-Butyldimethyl(((2R,3S)-2-((trityloxy)methyl)-2,3-dihydrofuran-3-yl)oxy)silane (**20a**).* **20a** was prepared according to the general procedure from **20** (1 mmol, 585 mg) to yield a colorless oil (400 mg, 85%). FT-IR (ATR, neat): 1610, 1450, 1250, 1080 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.79−7.06 (m, 15H), 6.59 (d, J = 2.5 Hz, 1H), 5.10 (t, J = 2.6 Hz, 1H), 4.89 (t, J = 2.4 Hz, 1H), 4.37 (td, J = 5.2, 3.1 Hz, 1H), 3.19 (h, J = 5.5 Hz, 1H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 149.6, 144.5, 129.2, 128.5, 128.4, 127.7, 127.6, 104.3, 88.6, 77.0, 64.4, 26.2, 18.5, −4.0, −4.2. HRMS (ESI/FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{30}H_{36}NaO_3Si^+$ 495.2326; found 495.2323.

*(S)-tert-Butyl((2,3-dihydrofuran-2-yl)methoxy)diphenylsilane (**22a**).* **22a** was prepared according to the general procedure from **22** (0.6 mmol, 279 mg). The crude reaction mixture was directly purified by column chromatography on silica gel with hexanes and 1% triethylamine, to yield a colorless oil (186 mg, 92%). FT-IR (ATR, neat): 1620, 1425, 1120, 1050 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) δ 7.84−7.24 (m, 10H), 6.28 (q, J = 2.4 Hz, 1H), 4.87 (q, J = 2.5 Hz, 1H), 4.66 (ddt, J = 10.5, 7.3, 5.3 Hz, 1H), 3.86−3.60 (m, 1H), 2.65 (ddt, J = 15.2, 10.5, 2.3 Hz, 1H), 2.46 (ddt, J = 15.2, 7.4, 2.4 Hz, 1H), 1.06 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2) δ 145.6, 136.2, 135.5, 134.3, 130.2, 128.2, 99.6, 81.9, 66.6, 31.7, 27.2, 19.7.

*tert-Butyl((2S,3S)-2-(hydroxymethyl)-2,3-dihydrofuran-3-yl)carbamate (**24a**).* **24a** was prepared according to the general procedure from **24** (1 mmol, 485 mg) to yield a yellow oil (157 mg, 73%). FT-IR (ATR, neat): 1710, 1695, 1380, 1250, 1055 cm^{-1}. ^1H NMR (400 MHz, CD_2Cl_2) (rotamers) δ 6.71−6.24 (m, 1H), 4.95 (t, J = 2.2 Hz, 1H), 4.86−4.48 (m, 2H), 4.41−4.13 (m, 1H), 3.92−3.60 (m, 2H), 1.46 (s, 9H), 0.16 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, CD_2Cl_2) (rotamers) δ 149.41, 147.92, 102.06, 101.03, 89.58, 85.89, 80.58, 64.38, 60.31, 28.70, 27.74, 1.86, −0.23. HRMS (ESI/FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{13}H_{25}NNaO_4Si^+$ 310.1445; found 310.1447.

*Trimethyl(((2R,3R)-2-((trityloxy)methyl)-2,3-dihydrofuran-3-yl)oxy)silane (**25a**).* **25a** was prepared according to the general procedure from **25** (1 mmol, 485 mg) to yield a colorless oil (356 mg, 83%). FT-IR (ATR, neat): 1610, 1490, 1450, 1250, 1050 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ 7.76−7.10 (m, 15H), 6.61 (d, J = 2.6 Hz, 1H), 5.07 (t, J = 2.6 Hz, 1H), 4.79 (dd, J = 6.7, 2.5 Hz, 1H), 4.40 (td, J = 8.0, 3.4 Hz, 1H), 3.42 (dd, J = 10.7, 8.3 Hz, 1H), 3.23 (dd, J = 10.7, 3.4 Hz, 1H), −0.08 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 150.0, 144.7, 129.3, 128.4, 127.6, 104.6, 84.6, 73.7, 63.2, 0.1. HRMS (ESI/FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{27}H_{30}NaO_3Si^+$ 453.1856; found 453.1853.

*(6aR,9aS)-2,2,4,4-Tetraisopropyl-9-methyl-6a,9a-dihydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocine (**30a**).* **30a** was prepared according to the general procedure from **30** (0.725 mmol, 352 mg) to yield a colorless oil (188 mg, 70%). FT-IR (ATR, neat): 1680, 1465, 1080 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2) δ 6.15 (s, 1H), 5.07 (d, J = 4.3 Hz, 1H), 4.38 (dt, J = 10.9, 4.6 Hz, 1H), 4.13 (dd, J = 11.0, 4.6 Hz, 1H), 3.65 (t, J = 11.1 Hz, 1H), 1.71 (s, 3H), 1.36−0.96 (m, 28H). $^{13}C\{^1H\}$ NMR (126 MHz, CD_2Cl_2) δ 142.0, 111.5, 88.4, 80.5, 64.4, 29.0, 17.4, 17.3, 17.2, 17.0, 16.9, 16.7, 16.7, 13.9, 13.7, 13.6, 13.2, 12.5. HRMS (ESI/FT-ICR) m/z: $[M + Na]^+$ calcd for $C_{18}H_{36}NaO_4Si_2^+$ 395.2044; found 395.2043.

*Larger-Scale Preparation of Trimethyl(((2R,3S)-3-((trimethylsilyl)oxy)-2,3-dihydrofuran-2-yl)methoxy)silane (**1**).* Thymidine (121 g, 500 mmol), *N*-(diphenylphosphorothioyl)-*P*,*P*-diphenylphosphinothioic amide (**5a**, $[Ph_2PS]_2NH$, 2.22 g, 5.00 mmol), 2,6-lutidine (29.1 mL, 250 mmol), heptane (847 mL), and

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toluene (363 mL) were added to a 5 L three-necked RB flask that was equipped with a nitrogen inlet adapter, a thermocouple probe, and a mechanical stirrer. The mixture was heated in an oil bath at 102 °C (internal temperature). *N,O*-Bis(trimethylsilyl)acetamide (208 mL, 2.13 mmol) was added dropwise over 25 min via an addition funnel; the mixture became homogenous 25 min after the end of addition. After 3 h at 99−103 °C, NMR analysis indicated <0.5% thymidine and 100% assay yield (using 2,6-lutidine as an internal standard). The reaction mixture was transferred dropwise to *i*PrOH (308 mL, 4.00 mol) in another 5 L three-necked RB flask, which was heated in an oil bath set at 52 °C and equipped with a nitrogen inlet adapter, thermocouple probe, and mechanical stirrer at 7.5 cc per minute over 4 h via a programmable Vaportech V3 pump with a bath. The resulting slurry was maintained at 50−51 °C for 1.5 h. The mixture was cooled to 10 °C over 1 h and filtered on a sintered glass filter funnel. The filter cake was washed with heptane (605 mL). The combined filtrates were filtered through a plug of neutral alumina (activated Brockmann 1, 42 g), washing the plug with heptane (75 mL). The filtrate was concentrated to ca. 300 mL volume; NMR analysis indicated a 98% assay yield (relative to the added trimethylmethane internal standard). The concentrated solution was fractionally vacuum distilled (0.1 mm Hg) using a vacuum jacketed Vigreux distilling head (Chemglass CG-1247-09). The first fraction boiling at <30 °C consisting of heptane, *i*PrOTMS, and 2,6-lutidine was collected in a receiver and cooled in a dry ice acetone bath. The second fraction boiling at 30−55 °C consisting of 2,6-lutidine, a small amount (<3 mol %) of the TMS ether of furfuryl alcohol, and a trace (<3 mol %) of **1** was collected in a receiver and cooled to −20 °C. The third fraction boiling at 55−75 °C consisting of glycal **1** with 1 mol % 2,6-lutidine (124.7 g, 95% of glycal **1**) was collected as a colorless liquid in a receiver and cooled to 0 °C. The distillation residue consisted of mostly the catalyst **5a**.

*N-(Diphenylphosphorothioyl)-P,P-diphenylphosphinothioic Amide, [Ph_2PS]$_2$NH (**5a**).* *N,N*-Bis(diphenylphosphino)amine (5.01 g, 13.0 mmol, Strem Chemicals, Inc.), sulfur (0.834 g, 26.0 mmol), and toluene (20 mL) were heated to 100 °C for 16 h giving a white suspension. This was allowed to cool to 25 °C over 2 h. Hexane (10 mL) was added, and the mixture was stirred for 1 h. The white solid was filtered off; washed with CS_2 (15 mL) to remove sulfur, toluene (15 mL), and finally hexane (20 mL); and dried under a nitrogen stream to provide **5a** (5.26 g, 92% yield) as a white crystalline solid. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.94−7.85 (m, 8H), 7.49−7.46 (m, 4H), 7.39−7.36 (m, 8H), 4.51 (br s, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 134.0 (dd, J_{C-P} = 106.2, 2.6 Hz), 132.3 (m), 128.6 (t, J_{C-P} = 6.8 Hz). ^{31}P NMR (203 MHz, CD_2Cl_2) δ 56.1.

*N-(Diphenylphosphorothioyl)-P,P-diphenylphosphinoselenoic Amide, [Ph_2PSe]$_2$NH (**5b**).* Sodium bisulfite (81.0 g, 780 mmol) was dissolved in water (300 mL) and was added dropwise over 2 h to a magnetically stirred solution of selenium dioxide (36.1 g, 325 mmol) in water (600 mL) in a 1 L Wheaton bottle open to the air in an ice bath. The internal temperature did not exceed 12 °C during addition. The mixture was allowed to warm to room temperature overnight. The originally colorless solution gradually turned yellow and darkened ultimately depositing amorphous selenium as a brick-red solid. If this mixture was allowed to heat up >70 °C during the addition, the precipitated selenium turns to a much denser less reactive black solid. The brick-red solid was filtered off and washed with water (200 mL), then acetone (100 mL), and finally (100 mL) hexane. The solid was dried under a nitrogen stream to give red amorphous elemental selenium (23.5 g). *N,N*-Bis(diphenylphosphino)amine (5.01 g, 13.0 mmol, Strem Chemicals, Inc.), red amorphous selenium (2.05 g, 26.0 mmol), and toluene (20 mL) were heated gradually up to 100 °C over 6 h. The suspension was stirred at 100 °C for 20 h giving a white suspension. This was allowed to cool to 25 °C over 2 h. Hexane (10 mL) was added, and the mixture was stirred for 1 h. The white solid was filtered off, washed with 1:1 toluene−hexane (15 mL) and hexane (20 mL), and dried under a nitrogen stream to provide **5b** (6.80 g, 96% yield) as a white crystalline solid. This material was stored under nitrogen in the dark in the freezer; otherwise, exposure to light and air resulted in the development of a pale pink color after several days. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.92−7.87 (m, 8H), 7.48−7.45 (m, 4H), 7.39−7.35 (m, 8H), 1.73 (br s, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 132.7 (dd, J_{C-P} = 97.9, 5.7 Hz), 132.1 (t, J_{C-P} = 6.5 Hz), 131.8 (t, J_{C-P} = 1.4 Hz), 127.9 (t, J_{C-P} = 6.5 Hz). ^{31}P NMR (203 MHz, CD_2Cl_2) δ 51.8 (d, J_{P-Se} = 792 Hz).

*(2R,3S,5R)-5-(5-Methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-((trityloxy)methyl)tetrahydrofuran-3-yl Pivalate (**21**).* To a round-bottom flask were added **19** (2.42 g, 5.00 mmol), pivalic anhydride (2.03 mL, 10.0 mmol, 2 equiv), DMAP (0.061 g, 0.500 mmol, 0.1 equiv), and pyridine (20 mL). The reaction was stirred for 24 h at room temperature. After reaction completion, as determined by TLC, ethyl acetate and saturated aqueous sodium bicarbonate were added. The layers were separated, and the aqueous layer was washed with ethyl acetate three times. The organic layers were combined and dried with anhydrous magnesium sulfate. The solution was concentrated to give a clear oil. The crude mixture crystallized on standing overnight. The crystals were washed with water and hexane to give product **21** (2.56 g, 90%) as a crystalline white solid. mp = 127−130 °C. FT-IR (ATR, neat): 1725, 1705, 1680, 1440, 1160 cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN) δ 9.25 (s, 1H), 7.52 (s, 1H), 7.48 (d, J = 7.3 Hz, 6H), 7.34 (dt, J = 27.7, 7.3 Hz, 9H), 6.31 (dd, J = 8.4, 6.0 Hz, 1H), 5.43−5.38 (m, 1H), 4.08 (q, J = 2.9 Hz, 1H), 3.43 (d, J = 6.8 Hz, 1H), 3.40−3.34 (m, 1H), 2.54−2.44 (m, 1H), 2.39 (ddd, J = 14.3, 5.9, 2.0 Hz, 1H), 1.49 (s, 3H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, CD_3CN) δ 179.1, 165.1, 152.0, 145.2, 137.0, 130.0, 129.5, 128.9, 112.1, 88.6, 85.7, 85.1, 75.8, 65.3, 39.7, 38.5, 27.7, 12.7. HRMS (ESI/FT-ICR) *m/z*: [M + Na]$^+$ calcd for $C_{34}H_{36}N_2NaO_6^+$ 591.2466; found 591.2462.

*1-((2R,5S)-5-(((tert-Butyldiphenylsilyl)oxy)methyl)-tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**22**).* In a dry round-bottom flask equipped with a magnetic stir bar, 2′,3′-dideoxythymidine (500 mg, 2.21 mmol), DMAP (13.5 mg, 0.111 mmol, 0.05 equiv), *tert*-butylchlorodiphenylsilane (690 μL, 2.65 mmol, 1.2 equiv), and DMF (5 mL) were added. The reaction was stirred for 24 h at room temperature, and reaction progress was monitored by HPLC. Upon completion, the reaction was extracted with ethyl acetate and water, and the organic layer was washed with aqueous sodium bicarbonate, followed by water and brine. The organic phase was dried over anhydrous magnesium sulfate and evaporated to give the crude product, which was purified by flash chromatography (50:50 hexanes/ethyl acetate) to give the product **22** as a clear oil (964 mg, 94%). NMR data was consistent with the literature.[16]

*1-((6aR,8R,9aS)-2,2,4,4-Tetraisopropyl-9-methyltetrahydro-6H-furo[3,2-f][1,3,5,2,4]trioxadisilocin-8-yl)pyrimidine-2,4(1H,3H)-dione (**30**).* In a dry 100 mL three-necked round-bottom flask, **30b**[17] (1.00 g, 2.07 mmol), 10% palladium on carbon (200 mg), and methanol (50 mL) were added. The flask was vacuumed and backfilled with nitrogen three times with stirring. A hydrogen balloon was attached, and the flask was vacuumed and backfilled with hydrogen three times and then filled with hydrogen. The reaction was stirred at room temperature and atmospheric pressure for 3 h, after which the reaction was deemed complete by HPLC. The reaction was filtered through a Celite pad and washed with methanol. The solution was concentrated to give the crude product **30**, which was purified by column chromatography (50:50 hexanes/ethyl acetate) to give the product as a clear oil and a 1.9:1 mixture of diastereomers (900 mg, 90%). FT-IR (ATR, neat): 1695, 1465, 1390, 1260, 1035 cm^{-1}. ^{1}H NMR (400 MHz, CD_3CN) δ 9.18 (br s, 1H), 7.68 (major, d, J = 8.1 Hz, 1H), 7.63 (minor, d, J = 8.1 Hz, 1H), 7.25 (minor, m, 1H), 6.17 (major, d, J = 7.4 Hz, 1H), 5.66 (minor, d, J = 3.6 Hz, 1H), 5.62 (major, d, J = 8.1 Hz, 1H), 5.47 (minor, t, J = 7.5 Hz, 1H), 4.23−3.90 (m, 3H), 3.79 (major, d, J = 8.5 Hz, 1H), 2.72−2.59 (major, m, 1H), 2.42 (minor, td, J = 7.3, 3.6 Hz, 1H), 1.18−0.96 (m, 32H). ^{13}C{^{1}H} NMR (101 MHz, CD_3CN) δ 163.1, 162.9, 150.6, 150.5, 140.2, 139.7, 117.3, 101.3, 89.8, 85.6, 83.8, 83.1, 73.0, 70.1, 61.5, 60.1, 44.0, 42.4, 16.9, 16.9, 16.8, 16.7, 16.7, 16.6, 16.5, 16.5, 16.5, 16.4, 13.5, 13.2, 12.9, 12.8, 12.8, 12.7, 12.5, 12.4, 10.7, 10.1. HRMS (ESI/FT-ICR) *m/z*: [M + Na]$^+$ calcd for $C_{22}H_{40}N_2NaO_6Si_2^+$ 507.2317; found 507.2314.

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Synthesis of Glycal 1 from Thymidine Using $(PhSO_2)_2NH$ as a Catalyst and Isolation of the Bis-Glycosylated Byproduct. A mixture of thymidine (3.63 g, 15.0 mmol), dibenzenesulfonimide, $(PhSO_2)_2NH$ (44.6 mg, 0.15 mmol), HMDS (12.7 mL, 60.0 mmol), Et_3N (21.0 μL, 0.150 mmol), and heptane (36 mL) was heated to reflux under nitrogen (with allowance for escape of ammonia via a bubbler) for 18 h to give homogenous amber solution. HPLC indicated >99% conversion, and the mixture was cooled to 20 °C. 2,4,6-Collidine (1.00 mL, 7.5 mmol) and *i*PrOH (0.193 mL, 2.500 mmol) were added, and the mixture was stirred for 1 h. Ethanol (0.730 mL, 12.50 mmol) was added over 40 min, and the mixture was stirred for 1 h. The resulting slurry was filtered, and the filter cake was washed with heptane (15 mL). The filter cake was dried under a nitrogen stream to provide thymine (1766 mg, 14.00 mmol, 93% yield). The filtrate was concentrated at <30 °C under vacuum (<5 torr) to 5 mL of a yellow oily residue. The residue was distilled under a rotary vane oil pump vacuum (0.04−0.03 Torr) with an oil bath at 100 °C during a 10 min period. The distillate was collected in a receiver cooled in an ice bath to give glycal **1** as a colorless mobile liquid (3.11 g, 80 wt % pure by NMR with 20 wt % collidine, 9.56 mmol, 64% yield). A viscous pale amber gummy distillation residue remained (815 mg) in the receiver. A stream of nitrogen was passed over the residue with stirring at 50 °C for 60 h to remove any remaining collidine and glycal to provide the bis-glycosylated byproduct as a gum (781 mg, 16%) containing some polymeric materials (as shown by DOSY NMR) for analysis. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.70 (m, 1H), 6.19 (m, 1H), 4.45 (m, 1H), 4.28 (m, 1H), 3.85−3.65 (m, 6H), 2.73 (m, 1H), 2.17 (m, 2H), 1.97 (m, 1H), 1.81 (s, 3H), 0.10−0.01 (m, 36H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 163.0, 150.3, 133.9, 109.9, 87.4, 87.3, 85.5, 82.3, 72.7, 71.2, 63.6, 61.7, 41.2, 37.7, 13.3, 0.0, −0.1, −0.5, −0.7. HRMS (ESI/FT-ICR) *m/z*: $[M + Na]^+$ calcd for $C_{27}H_{54}NaO_8Si_4^+$ 669.2855; found 669.2855.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00555.

Characterizations of **1**, **5a**, **5b**, **13a**−**30a**, **21**, **22**, **30**, and bis-glycosylated byproduct; computational data for **5a** and **5b** (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(7) The bisglycosylated byproduct is presumably formed by reaction of thymidine with the intermediate oxonium ion **4** generating predominantly one diastereomer (ROESY). Some higher molecular weight species are also formed (DOSY).

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