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The Reactivity of Thymine and Thymidine 5,6-Epoxides with Organometallic Reagents – A Route to Thymidine (6-4) Photoproduct Analogues

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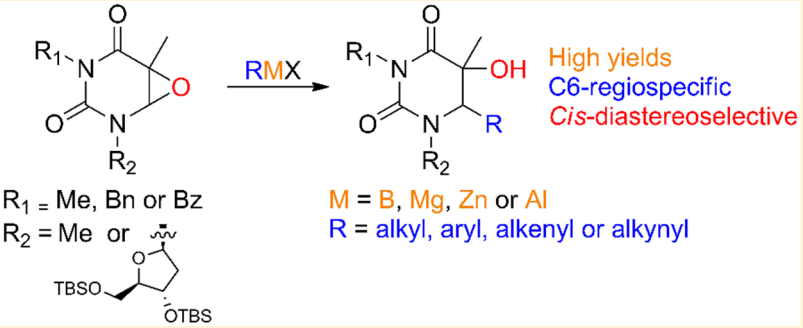
Supporting Information



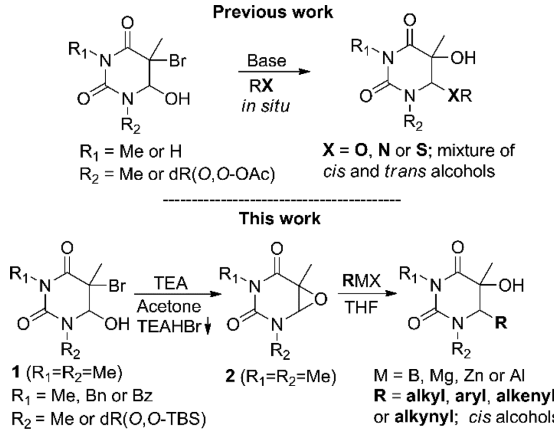
ABSTRACT: This report describes an efficient procedure for the generation and isolation of various thymine and thymidine 5,6-epoxides from the corresponding *trans*-5,6-bromohydrins by reaction with triethylamine. The quantitative isolation of the epoxides, accomplished by solvent precipitation of triethylamine hydrobromide, enabled their regiospecific ring-opening at C6 position by organometallic nucleophiles. The reaction was amenable to a broad range of alkyl, aryl, alkenyl, and alkynyl organomagnesium, -zinc, -aluminum, or -boron reagents, although the reactivity was strongly affected by the electronic effects of N3 protecting group. Additionally, the reaction featured excellent *cis*-diastereoselectivity providing access to C6-carbon-functionalized dihydrothymidine *cis*-alcohols, which are synthetic derivatives of UV-induced DNA lesions, namely, thymidine (6-4) photoproducts.

INTRODUCTION

Thymine nucleobase and nucleoside analogues have an important role in the field of drug development[1] and in the studies of DNA strand breaking.[2] Thymine glycol (5,6-dihydroxy-5,6-dihydrothymine) and its deoxyribonucleoside are among the major products resulting from oxidative damage of DNA.[3] On a preparative scale, thymine glycols and the analogous thio, alkoxy, and amine alcohols can be synthesized regiospecifically at the C6 site of the thymine core, starting from the thymine *trans*-bromohydrins in the presence of bases (Scheme 1).[4] Thymine epoxide is postulated to be the key intermediate in these transformations,[4a,b,5] and its existence was confirmed by a ^{18}O-labeled oxygen migration study, in which the transfer of the hydroxyl group from C6 to C5 atom of 1,3-dimethylthymine bromohydrin was observed.[6] Thymine and thymidine epoxides are also considered to react with nucleophiles, such as, the amino acids and purines present in human body, and thus their synthesis has been explored[4a,7]

In contrast to the dihydrothymine C6-thio-, C6-alkoxy-, and C6-aminoalcohols, only a few examples of the respective C6 carbon-functionalized alcohols exist, presumably due to the challenges in their preparation, i.e., selective carbon derivatization of the nucleobase core. To date, C6 alkyl- or C6 aryl-substituted dihydrothymine alcohols have been obtained merely by photochemical reactions including γ-irradiation-initiated

Scheme 1. Isolation of Pyrimidine 5,6-Epoxides Permits Their Manipulation with Organometallic Nucleophiles



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radical oxidation and UV-irradiation in aqueous media, with or without additional oxidants.[5a,7b,8] This class of compounds is attractive in view of drug development and due to the importance of the photochemical formation of nucleic acid−protein cross-linkages in biological systems.[7c,9] Additionally, dimeric dihydrothymidine alcohols have an important role in the development of skin cancer, which is due to dimerization of adjacent thymine residues in DNA upon its exposure to sunlight (Figure 1).[10] This lesion interferes with DNA replication and transcription and may lead to mutation and cell death.[11] In humans, damaged DNA lesions are repaired through complex enzymatic processes, known as nucleotide excision repair mechanism (NER).[12]

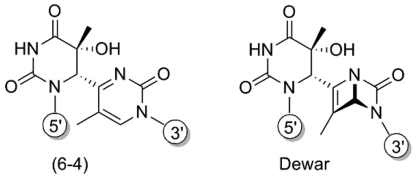


Figure 1. Major type of thymidine photoproduct (6-4) and its highly mutagenic Dewar-type isomer, triggered by UV irradiation of genomic DNA.

Owing to the biological significance of C6 carbon-substituted dihydrothymine and thymidine *cis*-alcohols, which cover all organisms,[13] a generic synthesis of their derivatives is of importance. Herein, we report an efficient method for the generation and isolation of dimethylthymine and various N3-protected thymidine 5,6-epoxides and detail their use as key intermediates to introduce carbon−carbon link at C6 into nucleobase core by epoxide ring opening with organometallic reagents.

RESULTS AND DISCUSSION

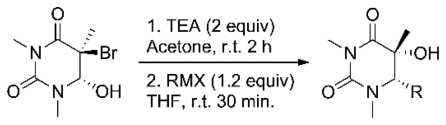
We initiated the study by investigating the formation of 1,3-dimethylthymine 5,6-epoxide **2** from bromohydrin **1** in the presence of triethylamine (TEA, Scheme 1). We found that the treatment of **1** with TEA in acetone generated **2** exclusively with full conversion of **1**, accompanied by a concurrent precipitation of triethylamine hydrobromide. The quantitative conversion also occurred in THF and MeCN, but the precipitation of triethylamine hydrobromide was not as efficient as in acetone; in which case the quantitative isolation of **2** from the reaction mixture was accomplished simply by filtering and subsequent evaporation of the solvent. In contrast, our attempts to isolate **2** after epoxidation of dimethylthymine with dimethyldioxirane (DMDO) in acetone[4e,14] proved unsuccesful.[15]

During investigation of its chemical behavior, we found that **2** was highly reactive toward nucleophiles, such as water, alcohols, and amines, forming thymine glycol, 6-alkoxy, and 6-amino alcohols (mixtures of *cis* and *trans* isomers), respectively, which was in agreement with earlier reports.[4] The epoxide was not stable if stored for a prolonged time (7 days at room temperature) in acetone under inert atmosphere. Also, attempts to further purify **2** by column chromatography led to its decomposition. However, as freshly prepared, **2** appeared to be a versatile substrate for the regiospecific introduction of a carbon−carbon bond into the thymine core by organometallic reagents, thus, enabling the synthesis of an array of new thymine derivatives.

To establish the scope of the reaction with organometallic reagents, we developed a standard experimental procedure based on the preliminary experiments of **2** with vinylmagnesium bromide. From the initial experiments, it was important to add the Grignard reagent to the reaction mixture in one portion since the dropwise addition (over 10 min) decreased the product yield by approximately 50%. Additionally, we did not observe the formation of other regioisomers in any experiments (C5-substitution), according to NMR spectroscopic measurements of the crude and purified products.

The addition of *n*- and *sec*-alkyl Grignard reagents to **2** afforded C6 alkyl-substituted dihydrothymine *cis*-alcohols **3**−**6** and **12** in fair yields (Table 1, entries 1−4 and 15; for stereostructural determination see later in the text). Even the bulky *tert*-butylmagnesium bromide gave the corresponding alcohol **7** (entry 5). Surprisingly, we also detected the simultaneous formation of the 5-hydroxy-5,6-dihydrothymine byproduct,[16] which is presumably due to β-hydride transfer from *tert*-butylmagnesium bromide to **2**. The introduction of π-systems into the thymine core, using vinyl-, phenyl-, and 2-thienylmagnesium bromides, afforded the respective alcohols **8**−**10** in good yields (entries 6−8). Furthermore, the use of ethynylmagnesium bromide as a nucleophile gave dihydrothymine alcohol **11** (entry 9). The less reactive phenyl- and vinylzinc bromides also added to the epoxide affording **8** and **9** in good yields (entries 10 and 11). However, no reaction occurred with butylzinc bromide as a nucleophile (entry 12). In terms of product yields, the reaction performed well with trimethyl- and triphenylaluminum[17] and

Table 1. Scope of the Reaction With 1 (Only One Enantiomer Depicted)



Entry	RMX	Product	Yield (%)
1	MgBr	**3**	57
2	MgCl	**4**	64
3	MgBr	**5**	58
4	MgBr	**6**	60
5	MgBr	**7**	30
6	MgBr	**8**	62
7	MgBr	**9**	74
8	MgBr	**10**	73
9	MgBr	**11**	63
10	ZnBr	**9**	82
11	ZnBr	**8**	83
12	ZnBr	**4**	-
13	$(C_6H_5)_3Al$	**9**	79
14	$Al(CH_3)_3$	**12**	83
15	MgBr	**12**	67
16	$(C_6H_5)_3B$	**9**	90

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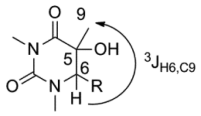
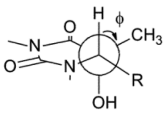
triphenylborane nucleophiles, resulting in phenyl- and methyl-substituted **9** and **12** in very good yields (entries 13, 15, and 16).

Before obtaining the crystal structures of **3** and **9**, confirming their *cis* configuration, we attempted to establish the diastereochemical arrangement of the products by ^{1}H−^{1}H NOESY NMR spectroscopy. Accordingly, gas-phase structures of *cis* and *trans* isomers of the starting material **1** and the products **3**−**11** were calculated using density functional theory (DFT) at the B3LYP/6-31(d) level. The computational results revealed a minimal distance difference of 0.1−0.3 Å existing between CH_3-9 and H6 in *cis* and *trans* isomers. The difference is too small to use NOESY to unambiguously distinguish the *cis* and *trans* configurations.[18] However, DFT models showed significant differences in H6−C6−C5-C9 torsion angles between the diastereomers and thus in the heteronuclear coupling constants between H6 and C9 ($^3J_{H6,C9}$). Therefore, we measured $^3J_{H6,C9}$ values for each derivative using the phase-sensitive, heteronuclear long-range coupling correlation NMR experiment, CBC-HSQMBC,[19] allowing for the extraction of $^nJ_{HC}$-values (n = 2−4) from the separation of antiphase lines in the correlation peak multiplets. Consequently, molecular dynamics simulations (MD) were performed for the products **1** and **3**−**11**, and the corresponding dihedral angles were transformed into heteronuclear coupling constants, using the Karplus equation (eq 1).[20] Comparison of these values, shown in Table 2, strongly suggests

Table 2. Experimental and Calculated Heteronuclear Coupling Constants (Hz) of Dihydrothymine Alcohols 1 and 3−11[a]





compd no.	exptl	$^3J_{H6,C9}$ (Hz) MD$_{cis}$	MD$_{trans}$
3	2.9	3.2	1.8
4	3.1	3.1	2.0
5	3.8	4.1	1.6
6	4.9	4.2	1.6
7	3.6	4.0	1.8
8	3.8	3.6	1.6
9	4.3	4.8	1.1
10	3.9	4.4	1.4
11	4.6	3.6	2.0
1	2.1	2.9	2.0

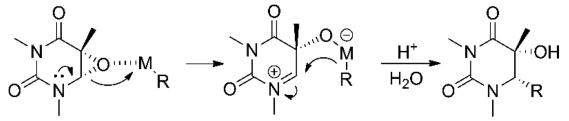
[a]MD = Molecular dynamics calculations.

the *cis* diastereochemical arrangement for thymine alcohols **3**−**11**. Moreover, the experimental and calculated $^3J_{H6,C9}$ couplings in bromohydrin **1** are in agreement with its structure, which is well established to possess a *trans* configuration (Table 2).[6]

$$^3J_{CH} = 4.5 - 0.78\cos\varphi + 4.03\cos 2\varphi \quad (1)$$

The observed *cis* relative stereochemistry suggests that the epoxide opens prior to nucleophilic attack, similarly to the epoxide ring-openings of 2,3-piperidines with organozinc compounds[21] and glycals with Grignard[22] or organoaluminum reagents.[23] Consequently, it is evident that the reaction proceeds through an intramolecular nucleophilic attack of the coordinated organometallic reagent to the zwitterionic iminium ion, as illustrated in Scheme 2.

Scheme 2. Proposed Mechanism (Only One Enantiomer Depicted)

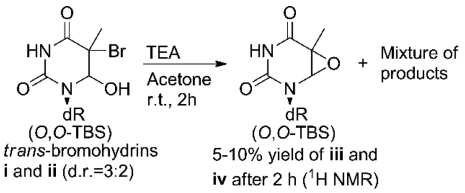


M = RMgBr, RZnBr, AlR_3 or BR_3

Next we applied the developed synthetic methodology, described above, to thymidine nucleoside, which provides access to a range of synthetic derivatives of thymidine photoproducts (Figure 1). These compounds can be highly useful in drug development, such as anticancer and antiviral agents,[1,24] and in mechanistic studies of DNA repair by NER[12a,c,d] or photolyases.[25] Additionally, they find application in the construction of fluorophores and chromophores to examine protein−protein and protein−ligand interactions.[26]

Initially, we studied the epoxide formation from *N*-H-*O*,*O*-TBS-dihydrothymidine bromohydrin (Scheme 3). The deoxy-

Scheme 3. Formation of Epoxides from N3-Unprotected Thymidine Bromohydrins



ribose (dR) alcohols were protected with *tert*-butyldimethylsilyl groups (TBS), which selective removal from thymidine is well-established,[27] by treating thymidine with TBS-Cl in the presence of pyridine and *N*,*N*-dimethylaminopyridine (DMAP). The bromohydrin formation with *N*-bromosuccinimide (NBS) in aqueous THF afforded a mixture of two *trans*-diastereomers (dr = 3:2, **i** and **ii**, Scheme 3).[4d] However, generation of the respective epoxides from both diastereomers independently using 1 equiv of TEA was low yielding (ca. 5−10% in 2 h, ^{1}H NMR, **iii** and **iv**, Scheme 3) and led to the formation of unidentified products, which did not react further in a desired manner. Even so, this could explain the excess of nucleophile (20 equiv) required for the efficient coupling of amines and amino acid ethyl esters with the *in situ* generated N3-unprotected thymidine epoxides[7a] and the contradictory results reported for the synthesis of dihydrothymidine aryl sulfides from the corresponding bromohydrins, in the presence of pyridine and zinc oxide.[4c,d]

As the protection of N3 was necessary, we chose to use the robust methyl group in order to prevent potential side reactions. Accordingly, N-methylation of *O*,*O*-TBS-thymidine with MeI in DMF in the presence of K_2CO_3[28] and the subsequent reaction with NBS in THF-H_2O gave dihydrothymidine *trans*-bromohydrins **13** and **14** (dr = 3:2), which were separated by flash column chromatography (Scheme 4).

When **13** was treated with triethylamine, the stereospecific elimination of HBr occurred as with bromohydrin **1**. This key step afforded thymidine epoxide **15** quantitatively, thus, opening the route for its efficient modification by organometallic reagents. The subsequent addition of phenylmagnesium bromide furnished C6 phenyl-substituted dihydrothymidine alcohol **17** as a single product in good yield. Likewise, the addition of

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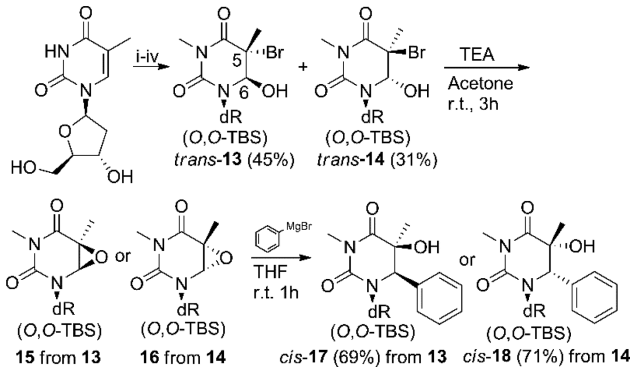
Scheme 4. Quantitative Stereospecific Formation of Thymidine Epoxides Followed by Regiospecific and Diastereoselective Addition of Phenylmagnesium Bromide[a]

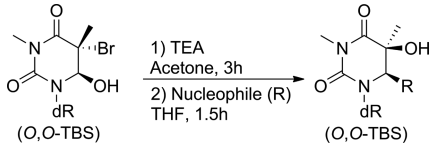


[a]Reagents and conditions: (i) TBS-Cl, pyridine, DMAP, DMF, 70 °C, 14 h; (ii) MeI, K_2CO_3, DMF, 40 °C, 12 h; (iii) NBS, NaCl(aq)-THF, rt, 40 min; and (iv) column chromatography.

phenylmagnesium bromide to the diastereomerically pure epoxide **16** afforded **18** as the sole product. The reaction also worked well when a mixture of **13** and **14** was used, albeit the separation of the diastereomers was somewhat more complex. The absolute configuration of **18** (5*R*, 6*S*) was established by a single-crystal X-ray structure determination, revealing its stereochemical resemblance to the UV-induced thymidine photoproducts shown in Figure 1. Due to the mechanistic aspects of the reaction (Scheme 2), the confirmed structure of **18** allowed us to determine the stereochemical arrangements of bromohydrins **13** (5*R*, 6*R*) and **14** (5*S*, 6*S*), as well as dihydrothymidine alcohol **17** (5*S*, 6*R*). Additionally, with thymidine bromohydrin **13** as a substrate, the reaction proved effective with a series of organomagnesium, -zinc and -aluminum reagents, providing C6-substituted *n*-butyl, isopropyl, 2-thienyl, phenyl, and ethynyl alcohols **19**, **20**, **21**, **17**, and **22** in fair to good yields, respectively (Table 3).

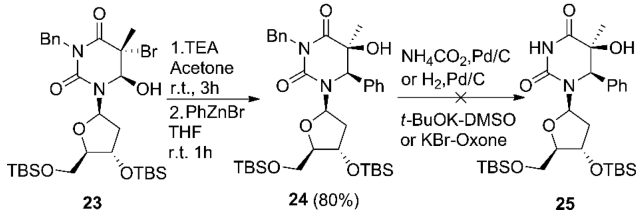
To evaluate the applicability of the method for thymidine with removable protecting group at N3, we prepared N3-benzyl-protected thymidine *trans*-bromohydrin **23** (major diastereomer, dr = 5:1, Scheme 5). The treatment of **23** with TEA followed by the addition of phenylzinc bromide afforded 6-phenyl

Table 3. Scope of the Reaction with Thymidine Bromohydrin 13



Entry	Nucleophile (R)	Product	Yield (%)
1	MgCl	**19**	36
2	MgBr	**20**	55
3	ZnBr	**17**	81
4	$(Ph)_3Al$	**17**	74
5	MgBr	**21**	71
6	MgBr	**22**	60

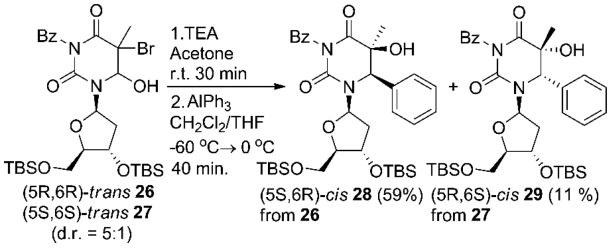
Scheme 5. Reaction Sequence with *N*-Benzyl Protected Thymidine and Efforts To Remove the Protecting Group



dihydrothymidine alcohol **24** in very good yield (80%). Unfortunately, all our efforts to remove the benzyl protecting group with NH_4CO_2-Pd/C,[29] H_2-Pd/C, *t*-BuOK-DMSO,[30] or KBr-oxone[31] methods failed. Also, attempts to use benzyloxymethyl ether (BOM)[32] protecting group were unsuccessful, as the bromohydrin formation with NBS in H_2O-THF was sluggish and gave the product in low yield.

We then changed the N3-protecting group to benzoyl, which can be removed from thymidine under basic conditions.[33] The treatment of *O*,*O*-TBS-thymidine with benzoyl chloride in MeCN in the presence of TEA and pyridine and the subsequent bromination with NBS gave the corresponding *N*-Bz-*O*,*O*-TBS *trans* bromohydrins **26** and **27** (dr = 5:1, Scheme 6).

Scheme 6. Phenyl Addition to *N*-Benzoyl-Protected Thymidine Epoxides Generated from a Mixture of 26 and 27



The epoxidation of **26** or **27** was found to be significantly faster than for those of N-methylated **13** and **14** or benzylated **23** (5 min versus 2 h, 1.5 equiv of TEA), ascribed to the electron-withdrawing nature of the benzoyl group (EWG), reducing the electron density in the pyrimidine ring. As a result, the epoxide can be expected to be more electrophilic than the epoxides generated from **13**, **14**, and **23** with electron-donating groups (EDG) at N3, but organozinc reagents (PhZnBr, PhZnBr + BF_3·OEt_2, or diphenylzinc) did not react, and thymidine glycol was the major product obtained after quenching the reactions with water. Apparently, with N-benzoylated thymidine epoxide, stronger Lewis acidity (oxophilicity) of the organometallic reagent is required to facilitate the formation of a reactive iminium-alkoxide pair (Scheme 2). Grignard reagents proved incompatible, and, for example, the addition of 1 equiv of phenylmagnesium bromide to the epoxide generated from **26** resulted in several decomposition products, and only traces of **28** were observed among the crude products. Gratifyingly, organoaluminum compounds, which are easily accessible with various methods,[34] were amenable to the reaction and the addition of triphenylaluminum[17] to the mixture of epoxides from **26** and **27** gave 6-phenyl-substituted **28** and **29**, in good overall yields of 70% (diastereomers were separable by column chromatography, Scheme 6). Trimethylaluminum reacted also with the epoxide but resulted in the loss of TBS groups to some extent, thus necessitating other protecting groups, such as benzyl, in the

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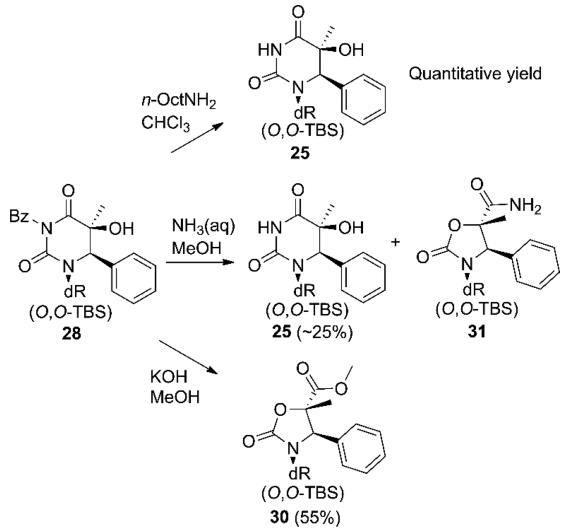
deoxyribose moiety. Additionally, arylboranes were compatible with the reaction as the addition of triphenylborane to **26** (90% diastereomeric purity) gave **28** in good 82% yield.

Several methods for quantitative N-debenzoylation of thymidine involve KOH-MeOH,[33b] NH_3(aq)-MeOH,[33a] and *n*- and *sec* alkylamines in various solvents.[33c] However, there are no examples in the literature describing the N3-debenzoylation of dihydrothymidines. In this respect, we were pleased to find that the treatment of **28** with 1.5 equiv of *n*-$BuNH_2$ for 1 h in $CHCl_3$ gave **25** regiospecifically and quantitatively, albeit we were not able to separate the formed products by column chromatography (*N*-butylbenzamide and **25**). By utilizing *n*-$OctNH_2$ in the reaction, the target product **25** was obtained in an excellent 97% yield after purification (Scheme 7). The absolute

Scheme 7. Regioselective N-Debenzoylation of 28 with *n*-$OctNH_2$ in $CHCl_3$ and Dihydropyrimidine Rearrangement to 2-Oxazolidone with KOH or Aqueous NH_3 in MeOH



configuration of **25** (5*S*, 6*R*) was confirmed by single-crystal X-ray structural determination (Figure S4 in Supporting Information), establishing also the stereochemical arrangements of **26** (5*R*, 6*R*), **27** (5*S*, 6*S*) and **29** (5*R*, 6*S*).

Unexpectedly, the treatment of **28** with KOH in MeOH (1 equiv, 20 min, rt) or aqueous NH_3 in MeOH (4 equiv, 1.5 h, rt) resulted in the dihydropyrimidine rearrangement, affording novel 2-oxazolidone derivatives **30** and **31** as major products; the former of which was purified and fully characterized (Scheme 7). Apparently, the presence of an ester bond at C4 in **30** indicates that the reaction proceeds through N3−C4 ring-cleaved methyl ester and amide intermediates, followed by cyclization and the loss of benzamide (for putative reaction mechanism; see Scheme S1 in Supporting Information). It is worth adding that the formation of 2-oxazolidone structure can be easily detected by ^{1}H NMR spectroscopy due to a notable shift in the singlet proton signal of the original dihydropyrimidine CH_3-7 from 1.9 to 1.0−1.1 in ppm ($CDCl_3$).

Evidently, in contrast to thymidine, the absence of the pyrimidine C5−C6 double bond and the resulting loss of ring aromaticity render dihydrothymidines susceptible to N3−C4 bond-cleavage by nucleophiles, through hemiaminal formation. This supplements recent observations that dimeric 5-thyminyl-5,6-dihydrothymine (spore photoproduct, SP)[35] and (6-4) photoproduct[36] undergo hydrolysis of N3−C4 bond in hot aqueous KOH, resulting in DNA strand break formation. Moreover, the N3−C4 bond cleavage by nucleophiles is enhanced by the presence of EWG groups, such as benzoyl at N3 (C4 more electrophilic), explaining the incompatibility of Grignard reagents with N3-Bz-protected dihydrothymidine epoxide (the reaction proceeded well with the respective electron-donating N3-Me and N3-Bn epoxides).

CONCLUSIONS

We have developed an efficient method for the generation and isolation of dimethylthymine and thymidine 5,6-epoxides from the corresponding bromohydrins. These epoxides were utilized, for the first time, in the regiospecific and stereoselective construction of carbon−carbon bonds at C6 of the nucleobase core using organometallic nucleophiles. The presented methodology possessed a broad substrate scope, performing well with various alkyl, alkenyl, aryl, and alkynyl organomagnesium, -zinc, -aluminum, or -boron reagents, especially with EDG protecting groups (Me and Bn) at N3. With EWG benzoyl group at N3 in thymidine the scope was more limited. This was due to the decreased reactivity of the epoxide and stability of the dihydropyrimidine ring, which makes the N3−C4 bond susceptible to cleaving by nucleophiles through hemiaminal formation. Regardless, the N3-Bz-dihydrothymidine epoxide was compatible with organoaluminum and arylboron reagents, and the quantitative Bz deprotection of the product was simply achieved by using primary alkylamines.

Notably, the procedure featured excellent *cis* diastereoselectivity enabling the stereoselective syntheses of C6-functionalized *cis*-5-hydroxy-5,6-dihydrothymidines. As analogues of thymidine (6-4) photoproducts, these compounds could be valuable, for example, in the studies of DNA repair and strand break formation and in drug development. Further expansion of the reaction scope on various N3-protected dihydrothymidine alcohols as well as the study of their dehydration to the respective C6-substituted nucleosides is underway in our laboratory.

EXPERIMENTAL SECTION

General Experimental Details. All manipulations were performed under argon atmosphere unless otherwise stated using Schlenk technique. All solvents were dried by using automated solvent purification system, except acetone which was dried over anhydrous $CaSO_4$ and distilled. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. HRMS measurements were carried out using either ESI-TOF or EI mass spectrometer. Melting points were determined with a capillary melting point apparatus and were uncorrected. FT-IR spectra of neat compounds were determined using FT-IR spectrometer equipped with a one reflection attenuated total reflection (ATR) unit. Absolute configuration of the products **3**, **9**, **18**, and **25** was determined by X-ray analysis (for detailed information; see Supporting Information). ^{1}H NMR and ^{13}C NMR spectra were acquired at 27 °C using 300 MHz (300 MHz ^{1}H-frequency and 75 MHz ^{13}C-frequency) or 500 MHz (500 MHz ^{1}H-frequency and 125.7 MHz ^{13}C-frequency) spectrometer. Chemical shifts are reported in ppm, and the ppm scale was referenced to residual solvent peaks ($CHCl_3$ in $CDCl_3$; 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C, acetone in acetone-d_6; 2.05 ppm for ^{1}H and 29.84 ppm for ^{13}C). Coupling constants are reported in Hz. ^{13}C NMR experiments were performed using APT pulse sequence (^{13}C{^{1}H} proton decoupling). The following abbreviations were used to describe the multiplicities of resonances: br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The 2D NMR experiments (HSQC and HMBC) were used as additional techniques for NMR signal assignments. All above-mentioned NMR spectra were processed with MestReNova 7.1.2.

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J. Org. Chem. 2016, 81, 3848−3859

CBC-HSQMBC.[37] All phase-sensitive CBC-HSQMBC-experiments were performed at 27 °C using 500 MHz spectrometer (500 MHz ^{1}H-frequency and 125.7 MHz ^{13}C-frequency) equipped with 5 mm PFG inverse-detection ^{1}H, X (X-coil tuned to ^{13}C) probehead capable of *z*-gradient amplitudes up to 20 G/cm. The spectral widths for ^{1}H- and ^{13}C-dimensions were 5006.25 and 29996.30 Hz, respectively. The CPMG-INEPT duration for polarization transfer via long-range couplings between ^{1}H and ^{13}C was optimized for $^nJ_{CH}$ = 8 Hz, whereas the CAGEBIRD^{r,X}-element duration was tuned according to $^1J_{CH}$ = 145 Hz. The 90° pulse widths for ^{1}H and ^{13}C were 7.0 and 11.7 μs, respectively. The simultaneous 180° ^{1}H and ^{13}C pulses in CPMG-pulsetrains were flanked by 100 μs delays (i.e., 200 μs interpulse delay). The relaxation delay was 1.0 s, and the number of transients was 16. Before the actual accumulation of data set, 64 steady-state scans were applied. The number of increments in the indirectly detected ^{13}C-dimension was 128. The number of acquired complex points was 5006 resulting in acquisition time of 1.0 s. All CBC-HSQMBC data were processed using NMR spectrometer operating software Vnmr 6.1C. The time-domain data in t_2-dimesion was apodized by shifted Gaussian function (gf = 0.259 s, gfs = 0.235 s) to improve the resolution, whereas unshifted Gaussian function was applied in t_1-dimension (gf1 = 0.00089 s). The data matrix was zero filled up to 8192(^{1}H) × 256(^{13}C) complex points prior to Fourier transform. The $^3J_{H6C9}$ values could be directly measured from the separation of antiphase lines in the ^{1}H-dimension of the relatively simple H_6C_9-correlation peak multiplets for the studied class of compounds.

DFT Calculations. Prior to the geometry optimization with DFT method, a conformational search for compounds **1** and **3**−**11** was performed with the semiempirical RM1 method. DFT calculations were performed using the B3LYP function in combination with the 6-31G* basis set as implemented in Spartan'10.

MD Calculations. MD calculations for the structures **1** and **3**−**11** were performed by following the specific dihedral angles (H6−C6−C5−C9) using the Hyperchem 8.0.4 software. All MD runs were done using following parameters: heat time 0 ps, run time 1 ps, cool time 0 ps, step size 0.001 ps, and constant temperature. Simulations were done at 27 °C in vacuo. The dihedral angles were transformed into heteronuclear coupling constants using eq 1.[20]

Synthesis of N,N-Dimethylthymine. The modified procedure described previously was used.[38] To a solution of thymine (10 g, 80 mmol) in DMF (120 mL) was added K_2CO_3 (38 g, 278 mmol, 3.5 equiv) and iodomethane (138 mmol, 15 mL, 3.0 equiv), and the resulting mixture was stirred at 50 °C for 48 h. Then water was added (300 mL), and the solution was extracted with chloroform (5 × 60 mL). The combined organic layers were washed with water (5 × 60 mL) and brine (1 × 60 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude title product as a white solid (8.6 g, 70%), which was used for the next step without further purifications. ^{1}H NMR (500 MHz, $CDCl_3$): 1.91 (d, *J* = 1.2 Hz, 3H), 3.33 (s, 3H), 3.35 (s, 3H), 6.97 (q, *J* = 1.2 Hz, 1H); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): 13.1, 28.0, 36.8, 109.7, 139.1, 152.0, 164.2.

*5-Bromo-6-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4-(1H,3H)-dione (**1**).* To a solution of dimethylthymine (5.0 g, 32 mmol) in THF (70 mL) was added water (14 mL) followed by the addition of bromine (2.1 mL, 42 mmol, 1.3 equiv) in small portions. The resulting solution was stirred at room temperature for 1 h (monitored by TLC; EtOAc:hexane 1:1), whereupon water (120 mL) and EtOAc (120 mL) were added, and the excess bromine was quenched by the addition of solid $Na_2S_2O_5$ in small portions under vigorous stirring until the solution became colorless. The organic phase was separated, and the water layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (2 × 60 mL), brine (60 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to yield the crude product, which was concentrated in EtOAc and precipitated by the addition of a mixture of diethyl ether/*n*-hexane (1:5 v/v to EtOAc) to afford racemic **1** (5.6 g, 70%) as a white powder. ^{1}H NMR (500 MHz, acetone-d_6); 1.93 (s, 3H); 3.11 (s, 3H); 3.12 (s, 3H); 5.06 (d, *J* = 5.5 Hz, 1H); 6.10 (d, *J* = 5.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (125.7 MHz, acetone-d_6): 24.4, 28.2, 34.9, 55.9, 86.1, 152.4, 168.3 ppm; IR (neat): 3327, 2945, 1718, 1677, 1652, 1487, 1292, and 1030 cm^{-1}; HRMS (EI) calcd for $C_7H_{11}BrN_2O_3$ (M^+) 249.9953, found 249.9965 (^{79}Br); calcd for $C_7H_{11}BrN_2O_3$ (M^+) 251.9933, found 251.9942 (^{81}Br); Mp 133 °C (dec.).

*2,4,6-Trimethyl-7-oxa-2,4-diazabicyclo[4.1.0]heptane-3,5-dione (**2**).* To a solution of **1** (0.50 g, 2.0 mmol) in dry acetone (7 mL) was added triethylamine (0.56 mL, 4.0 mmol, 2.0 equiv) at room temperature. The mixture was shaken and left standing, with gentle sporadic shaking, for 2 h to allow triethylamine hydrobromide precipitation. Then, the supernatant was transferred into another flask under inert atmosphere through a membrane filter (0.45 μm GHP ACRODISK 13). The remaining precipitate was washed once with dry acetone (1.5 mL), and filtering was repeated. The solution was evaporated under reduced pressure to afford the racemic title compound **2** as a colorless oil, which was used as such for the addition reactions. The NMR spectroscopic data reported here are not consistent with earlier reported data of **2**, prepared by direct epoxidation of dimethylthymine with $MeReO_3/H_2O_2$ or dimethydioxirane.[39] ^{1}H NMR (500 MHz, acetone-d_6, in 1 equiv of triethylamine): 1.52 (s, 3H), 3.10 (s, 3H), 3.19 (s, 3H), 4.84 (s, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, acetone-d_6, d1 = 15 s): 15.6, 28.2, 34.6, 56.0, 70.4, 152.1, 169.3 ppm; HRMS (EI) calcd $C_7H_{10}N_2O_3$ (M^+) 170.0691, found 170.0689.

General Procedure for the Addition of Grignard Reagents to 2. A Grignard reagent (2.4 mmol, 1.2 equiv) was added in one portion to a freshly prepared solution of **2** (2.0 mmol) in THF (7 mL) under argon. The resulting mixture was stirred at room temperature for 30 min, whereupon the reaction was quenched with sat. aq NH_4Cl (15 mL) and stirring was continued for 5 min. Then, the mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography.

*cis-6-Ethyl-5-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4-(1H,3H)-dione (**3**).* According to the general procedure, 0.8 mL of 3 M solution of ethylmagnesium bromide in diethyl ether was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:hexane 1:1 (v/v), R_f = 0.3) afforded the title product **3** as a white powder (227 mg, 57%). After recrystallization (*i*-PrOH-H_2O), the obtained transparent needles were dissolved in acetone, and single crystals suitable for X-ray crystallography were grown by slow evaporation of the solvent. ^{1}H NMR (500 MHz, $CDCl_3$): 0.92 (t, *J* = 7.5 Hz, 3H), 1.40−1.46 (m, 1H), 1.42 (s, 3H), 1.81−1.87 (m, 1H), 3.12 (s, 3H), 3.12−3.18 (m, 1H), 3.18 (s, 3H), 3.65 (br s, 1H, O*H*) ppm; ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): 10.8, 22.5, 26.3, 28.4, 37.6, 66.3, 71.0, 152.3, 175.0 ppm; IR (neat): 3437 (broad.), 2984, 2938, 1709, 1664, 1471, 1440, 1280, 1180, and 1075 cm^{-1}; HRMS (EI) calcd $C_9H_{16}N_2O_3$ (M^+) 200.1161, found 200.1160; Mp 77−78 °C.

*cis-6-Butyl-5-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4-(1H,3H)-dione (**4**).* According to the general procedure, 1.2 mL of 2 M solution of butylmagnesium chloride in THF was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by column chromatography (EtOAc:hexane 1:1.5 (v/v), R_f = 0.45) afforded the title product **4** as a white crystalline solid (292 mg, 64%) ^{1}H NMR (500 MHz, $CDCl_3$): 0.85−0.87 (m, 3H), 1.24−1.36 (m, 5H), 1.41 (s, 3H), 1,76−1.81 (m, 1H), 3.15−3.18 (m, 1H), 3.18 (s, 3H), 3.68 (br s, 1H, O*H*) ppm; ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$): 14.0, 23.0, 25.9, 28.2, 28.5, 29.2, 37.3, 65.0, 71.0, 152.2, 175.1 ppm; IR (neat): 3438 (broad), 2957, 2930, 2862, 1712, 1661, 1466, 1283, and 1054 cm^{-1}; HRMS (EI) calcd $C_{11}H_{20}N_2O_3$ (M^+) 228.1474, found 228.1463; Mp 72−73 °C.

*cis-5-Hydroxy-6-isopropyl-1,3,5-trimethyldihydropyrimidine-2,4-(1H,3H)-dione (**5**).* According to the general procedure, 1.2 mL of 2.0 M solution of isopropylmagnesium chloride in diethyl ether was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:hexane 1:1 (v/v), R_f = 0.3) afforded the title product **5** as a white powder (248 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): 0.76 (d, *J* = 6.9 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 1.42 (s, 3H), 2.24−2.30 (m, 1H), 3.14 (s, 3H), 3.15 (d, *J* = 3.3 Hz, 1H), 3.16 (s, 3H),

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J. Org. Chem. 2016, 81, 3848−3859

3.70 (br s, 1H, OH) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): 17.1, 22.0, 27.5, 28.1, 29.2, 39.1, 70.1, 70.3, 152.7, 175.2 ppm; IR (neat): 3397, 2965, 1704, 1656, 1473, 1281, 1175, and 1049 cm^{-1}; HRMS (EI) calcd for $C_{10}H_{18}N_2O_3$ (M^+) 214.1317, found 214.1309; Mp 73−74 °C.

*cis-6-Cyclohexyl-5-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4(1H,3H)-dione (**6**).* According to the general procedure, 1.2 mL of 2.0 M solution of cyclohexylmagnesium bromide in diethyl ether was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:hexane 1:2 (v/v), R_f = 0.25) afforded the title product **6** as a colorless oil. Crystallization from *i*-prOH/H_2O gave **6** as transparent needles (305 mg, 60%). ^1H NMR (500 MHz, $CDCl_3$): 0.95−1.23 (m, 5H), 1.35 (m, 1H), 1.42 (s, 3H), 1.62−1.73 (m, 4H), 1.88−1.96 (m, 1H), 3.09 (d, *J* = 3.5 Hz, 1H), 3.13 (s, 3H), 3.17 (s, 3H), 3.66 (s, 1H, OH) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): 26.2, 26.5, 27.0, 27.4, 27.5, 28.1, 32.5, 39.1, 39.3, 70.08, 70.14, 152.7, 175.3 ppm; IR (neat): 3369 (br.), 2931, 2855, 1702, 1660, 1447, 1281, and 1071 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}N_2O_3$ (M^+) 254.1630, found 254.1624; Mp 105−106 °C.

*cis-6-(tert-Butyl)-5-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4(1H,3H)-dione (**7**).* According to the general procedure, 1.2 mL of 2 M solution of *tert*-butylmagnesium chloride in diethyl ether was added in one portion to the previously prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:hexane 1:1.5 (v/v), R_f = 0.5) afforded the title product **7** as a white solid (132 mg, 30%). ^1H NMR (500 MHz, $CDCl_3$): 1.00 (s, 9H), 1.42 (s, 3H), 3.02 (s, 1H), 3.14 (s, 3H), 3.17 (s, 3H), 3.72 (br s, 1H, O*H*) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): 28.0, 28.4, 28.7, 37.7, 40.9, 71.7, 73.3, 152.7, 175.7 ppm; IR (neat): 3442 (broad), 2957, 2914, 2875, 1710, 1657, 1468, 1394, 1287, and 1054 cm^{-1}; HRMS (EI) calcd $C_{11}H_{20}N_2O_3$ (M^+) 228.1474, found 228.1474; Mp 75−76 °C.

*cis- 5-Hydroxy-1,3,5-trimethyl-6-vinyldihydropyrimidine-2,4-(1H,3H)-dione (**8**).* According to the general procedure, 2.4 mL of 1.0 M solution of vinylmagnesium bromide in THF was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:hexane 1:1.5 (v/v), R_f = 0.3) afforded the title product **8** as a white solid (245 mg, 62%). ^1H NMR (500 MHz, $CDCl_3$): 1.50 (s, 3H), 3.08 (s, 3H), 3.19 (s, 3H), 3.56 (s, 1H, O*H*), 3.72 (dt, *J* = 5.7, 1.3 Hz, 1H), 5.06−5.14 (m, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 5.80 (ddd, *J* = 17.1, 10.5, 5.7 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): 25.9, 28.3, 35.6, 66.5, 71.5, 118.3, 130.9, 152.6, 174.1 ppm; IR (neat): 3451 (broad), 2980, 1712, 1668, 1467, 1397, 1152, and 1072 cm^{-1}; HRMS (EI) calcd for $C_9H_{14}N_2O_3$ (M^+) 198.1004, found 198.1009; Mp 58−59 °C.

*cis-5-Hydroxy-1,3,5-trimethyl-6- phenyldihydropyrimidine-2,4-(1H,3H)-dione (**9**).* According to the general procedure, 0.8 mL of 3 M solution of phenylmagnesium bromide in diethyl ether was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:hexane 1:1.5 (v/v), R_f = 0.4) afforded the title product **9** as a colorless crystalline solid (357 mg, 74%). After recrystallization from *i*-PrOH-H_2O, the obtained transparent needles were dissolved in acetone, and single crystals suitable for X-ray crystallography were grown by slow evaporation of the solvent. ^1H NMR (500 MHz, $CDCl_3$): 1.64 (s, 3H), 3.05 (s, 3H), 3.28 (s, 4H), 4.25 (s, 1H), 7.04−7.06 (m, 2H), 7.31−7.32 (m, 3H) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): 27.3, 28.5, 35.8, 69.0, 71.2, 127.5, 128.70, 128.74, 134.1, 152.8, 173.8 ppm; IR (neat): 3403, 2991, 2938, 1713, 1659, 1448, 1182, 1170, and 1050 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{16}N_2O_3$ $(M)^+$ 248.1161, found 248.1174; Mp 114−115 °C.

*cis-5-Hydroxy-1,3,5-trimethyl-6-(thiophen-2-yl)dihydro-pyrimidine-2,4(1H,3H)-dione (**10**).* According to the general procedure, 2.4 mL of 1.0 M solution of 2-thienylmagnesium bromide in THF was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:$CHCl_3$ 1:4 (v/v), R_f = 0.35) afforded the title product **10** as a colorless oil (369 mg, 73%). ^1H NMR (500 MHz, $CDCl_3$): 1.61 (s, 3H), 3.11 (s, 3H), 3.25 (s, 3H), 3.49 (br s, 1H, -O*H*), 4.48 (s, 1H), 6.87−6.88 (d, *J* = 3.3 Hz, 1H), 6.95−6.97 (m, 1H), 7.26−7.27 (d, *J* = 4.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125.7, $CDCl_3$): 26.0, 28.5, 35.8, 65.2, 71.5, 126.6, 127.08, 127.14, 137.3, 152.6, 173.8 ppm; IR (neat): 3429 (broad), 2933, 1714, 1662, 1465, 1282, and 1044 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}N_2O_3S$ (M^+) 254.0725, found 254.0726.

*cis-6-Ethynyl-5-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4-(1H,3H)-dione (**11**).* According to the general procedure, 4.8 mL of 0.5 M solution of ethynylmagnesium bromide in THF was added in one portion to a freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by column chromatography (EtOAc:hexanes 1:1 (v/v), R_f = 0.4) afforded the title product **11** as a white powder (247 mg, 63%). ^1H NMR (500 MHz, $CDCl_3$): 1.49 (s, 3H), 2.38 (d, *J* = 2.1 Hz, 1H), 3.12 (s, 3H), 3.23 (s, 3H), 3.70 (s, 1H, O*H*), 3.94 (d, *J* = 2.1 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): 24.3, 28.6, 35.5, 57.4, 70.8, 75.1, 77.0, 152.7, 173.5 ppm; IR (neat): 3399 (broad), 3257, 3222, 2113, 1707, 1662, 1473, 1448, 1287, 1180, and 1054 cm^{-1}; HRMS (EI) calcd for $C_9H_{12}N_2O_3$ (M^+) 196.0848, found 196.0848; Mp 117 °C.

*cis-6-Ethyl-5-hydroxy-1,3,5-trimethyldihydropyrimidine-2,4-(1H,3H)-dione (**12**).* According to the general procedure, 0.8 mL of 3 M solution of methylmagnesium bromide in diethyl ether was added in one portion to the freshly prepared solution of 1.3-dimethylthymine epoxide **2** (2.0 mmol) in THF (7 mL). Purification by flash column chromatography (EtOAc:hexane 1:1 (v/v), R_f = 0.25) afforded the title product **12** as a colorless oil (248 mg, 67%). ^1H NMR (500 MHz, $CDCl_3$): 1.14 (dd, *J* = 6.7, 1.0 Hz, 3H), 1.45 (d, *J* = 0.9 Hz, 3H), 3.08 (d, *J* = 1.0 Hz, 3H), 3.21 (d, *J* = 1.0 Hz, 3H), 3.24−3.35 (m, 1H), 3.61 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$): 13.2, 25.6, 28.3, 35.6, 60.6, 71.3, 152.1, 174.7 ppm; HRMS (EI) calcd $C_8H_{14}N_2O_3$ (M^+) 186.1004, found 186.0999.

*Synthesis of **8** and **9** Using Zinc Nucleophiles.* Anhydrous zinc bromide (586 mg, 2.6 mmol) was dissolved in 4 mL of THF, and the solution was cooled to 0 °C using an ice bath. Next, 2.4 mL of 1.0 M solution of vinylmagnesium bromide in THF or 0.8 mL of 3 M solution of phenylmagnesium bromide in diethyl ether (2.4 mmol) was added, and the resulting white suspension was warmed to room temperature and stirred for 1 h. In a separate flask, freshly prepared epoxide **2** (1.99 mmol) was dissolved in 3 mL THF. The previously prepared zinc nucleophile was then transferred via cannula in one portion, and the mixture was stirred at room temperature for 30 min. The reaction was quenched by addition of saturated ammonium chloride (3 mL), and the zinc salts were dissolved upon addition of ammonium hydroxide 28% (10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by column chromatography eluting with EtOAc:hexane 1:1.5 to afford **8** as a white solid (329 mg, 83%, R_f = 0.3) or **9** as transparent solid (407 mg, 82%, R_f = 0.4), depending on the substrate. ^1H and ^{13}C NMR spectra of the products were identical to those of obtained above using Grignard reagents.

*Synthesis of **9** Using $AlPh_3$.* Triphenylaluminum was prepared by adding 1.05 mL of 3 M phenylmagnesium bromide in Et_2O (3.2 mmol) into a solution of 0.5 M $AlCl_3$ in THF (2.2 mL, 1.1 mmol) and stirred at room temperature for 16 h under argon.[17] In a separate flask, freshly prepared epoxide **2** (0.86 mmol) was dissolved in 3 mL THF. The previously prepared $AlPh_3$ solution was then transferred via cannula in one portion, and the mixture was stirred at room temperature for 0.5 h, whereupon the reaction was quenched by addition of saturated ammonium chloride (3 mL). EtOAc was added (40 mL), and the aluminum salts were dissolved upon addition of 1 M NaOH (10 mL). The organic layer was separated and washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (EtOAc:hexane 1:1.5 (v/v), R_f = 0.4) affording **9** as transparent solid (167 mg, 79%). ^1H and ^{13}C NMR spectra of the product were identical to those of obtained above using PhMgBr.

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J. Org. Chem. 2016, 81, 3848−3859

*Synthesis of **12** Using $AlMe_3$.* A 2 M solution of $AlMe_3$ (1.2 mL, 2.4 mmol) in toluene was added in one portion to a freshly prepared solution of **2** (1.99 mmol) in THF (7 mL) under argon. The resulting mixture was stirred at room temperature for 0.5 h, whereupon the reaction was quenched by addition of saturated ammonium chloride (5 mL). EtOAc was added (40 mL), and the aluminum salts were dissolved upon addition of 1 M NaOH (15 mL). The organic layer was separated and washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (EtOAc:hexane 1:1 (v/v), R_f = 0.25) affording **12** as colorless oil (308 mg, 83%). ^{1}H and ^{13}C NMR spectra of the product were identical to those of obtained using MeMgBr.

*Synthesis of **9** Using BPh_3.* To a freshly prepared solution of **2** (0.5 mmol) in THF (3 mL) under argon, 145 mg BPh_3 (0.6 mmol) was added. The resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with sat. aq $NaHCO_3$ (7 mL) and stirred for 10 min. Then, the mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (EtOAc:hexane 1:1.5 (v/v), R_f = 0.4) to afford **9** as a white solid (112 mg, 90%). ^{1}H and ^{13}C NMR spectra of the product were identical to those of obtained using PhMgBr or $AlPh_3$.

TBS Protection of Thymidine. To a solution of thymidine (4.0 g, 16.5 mmol) in DMF (50 mL) under argon were added *tert*-butyldimethylsilyl chloride (6.0 g, 40 mmol, TBS), pyridine (5.3 mL, 66 mmol), and 4-dimethylaminopyridine (DMAP, 0.2 g, 1.64 mmol). The resulting solution was stirred at 70 °C for 14 h. Then, water (120 mL) and EtOAc (250 mL) were added, and the organic layer was separated, washed with water (5 × 50 mL), brine (50 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford *O*,*O*-TBS-thymidine as a white solid (7.5 g, 96%), which was used for the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00−0.18 (m, 12H), 0.81−0.98 (m, 18H), 1.90 (d, *J* = 1.3 Hz, 3H), 1.99 (ddd, *J* = 13.1, 7.9, 6.1 Hz, 1H), 2.24 (ddd, *J* = 13.1, 5.9, 2.6 Hz, 1H), 3.75 (dd, *J* = 11.4, 2.5 Hz, 1H), 3.86 (dd, *J* = 11.4, 2.6 Hz, 1H), 3.92 (m, 1H), 4.39 (dt, *J* = 5.6, 2.6 Hz, 1H), 6.32 (dd, *J* = 7.9, 5.9 Hz, 1H), 7.46 (d, *J* = 1.3 Hz 1H), 9.02 (s, 1H,) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ −5.3, −5.2, −4.7, −4.5, −3.5, 12.7, 18.1, 18.5, 25.8, 25.8, 25.9, 26.1, 41.5, 63.1, 72.4, 85.9, 87.9, 111.0, 135.6, 150.5, 164.0 ppm.

N-Methylation of O,O-TBS-Thymidine. To a solution of *O*,*O*-TBS-thymidine (6 g, 12.7 mmol) in DMF (60 mL) under argon were added K_2CO_3 (4.5 g, 25 mmol) and iodomethane (1.2 mL, 19.1 mmol), and the resulting mixture was stirred at 40 °C for 12 h.[28] Next, ice-cold water (120 mL) and Et_2O (200 mL) were added, and the organic phase was separated, washed with water (3 × 50 mL) and brine (50 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give *N*-Me-*O*,*O*-TBS thymidine as a white solid (5.6 g, 95%), which was used for the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06−0.10 (m, 12H), 0.88 (s, 9H), 0.91 (s, 9H), 1.92 (d, *J* = 1.2 Hz, 3H), 1.95−2.04 (m, 1H), 2.26 (ddd, *J* = 13.1, 5.8, 2.7 Hz, 1H), 3.75 (dd, *J* = 11.3, 2.6 Hz, 1H), 3.86 (dd, *J* = 11.3, 2.6 Hz, 1H), 3.93 (m, 1H), 4.39 (dt, *J* = 5.6, 2.6 Hz, 1H), 6.35 (dd, *J* = 7.8, 5.8 Hz, 1H), 7.46 (d, *J* = 1.2 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.7, −4.5, 13.5, 18.1, 18.5, 26.0, 26.02, 28.0, 41.6, 63.1, 72.3, 85.7, 87.9, 110.0, 133.4, 151.4, 163.8 ppm.

*trans-Bromohydrins **13** and **14**.* To a solution of *N*-Me-*O*,*O*-TBS thymidine (1.0 g, 2.1 mmol) in THF (25 mL) under argon were added brine (15 mL) and H_2O (5 mL) followed by the addition *N*-bromosuccinimide (1.84 g, 10.3 mmol). The resulting biphasic solution was stirred vigorously at room temperature, and the reaction was monitored by TLC (EtOAc:hexane 1:7). After 45 min, water (30 mL) and EtOAc (60 mL) were added, and the excess bromine was quenched by the addition of solid $Na_2S_2O_5$ in small portions under vigorous stirring until the solution became colorless. The organic phase was separated, and the water layer was extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with sat. aq $NaHCO_3$ (30 mL), brine (30 mL), and dried over Na_2SO_4. The solvents were evaporated under reduced pressure to afford a crude mixture of diastereomers, which were separated and purified by column chromatography (EtOAc:hexane 1:7) to afford **13** (0.55 g, 45%, white solid, R_f = 0.30) and **14** (0.38 g, 31%, white solid, R_f = 0.20).

*trans-(5R,6R)-5-Bromo-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-hydroxy-3,5-dimethyldihydropyrimidine-2,4(1H,3H)-dione (**13**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.04−0.24 (m, 12H), 0.89 (s, 9H), 0.92 (s, 9H), 1.99 (s, 3H), 2.07−2.34 (m, 2H), 3.24 (s, 3H), 3.73 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.78 (dt, *J* = 4.3, 2.3 Hz, 1H), 3.84 (dd, *J* = 11.0, 2.4 Hz, 1H), 4.02 (d, *J* = 2.4 Hz, 1H, -O*H*), 4.34−4.49 (m, 1H), 5.06 (d, *J* = 2.4 Hz, 1H), 6.46−6.59 (t, *J* = 6.8 Hz 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.4, −5.3, −4.7, −4.3, 18.1, 18.7, 23.8, 25.9, 26.1, 28.6, 38.5, 53.6, 62.0, 71.0, 80.0, 85.2, 86.0, 151.8, 167.2 ppm; IR (neat): 3319, 2952, 2927, 2855, 1719, 1648, 1469, 1107, 1082, 1029, and 831 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{45}BrN_2NaO_6Si_2$ [M + Na]$^+$ 603.1892, found 603.1882. Mp 108−111 °C.

*trans-(5S,6S)-5-Bromo-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-hydroxy-3,5-dimethyldihydropyrimidine-2,4(1H,3H)-dione (**14**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07−0.12 (m, 12H), 0.88 (s, 9H), 0.92 (s, 9H), 1.97 (s, 3H), 2.26−2.45 (m, 2H), 3.20 (s, 3H), 3.71−3.83 (m, 1H), 3.90−4.01 (m, 2H), 4.34 (d, *J* = 5.1 Hz, 1H, -O*H*), 4.35−4.40 (m, 1H), 5.45 (d, *J* = 5.1 Hz, 1H), 5.87 (t, *J* = 6.0 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.4, −5.1, −4.7, −4.4, 18.1, 18.8, 23.8, 25.9, 26.2, 28.3, 41.8, 58.3, 63.3, 71.2, 79.2, 87.4, 87.5, 150.6, 167.5 ppm; IR (neat): 3393, 2955, 2929, 2857, 1717, 1672, 1463, 1109, 1074, 1027, and 832 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{45}BrN_2NaO_6Si_2$ [M + Na]$^+$ 603.1892, found 603.1900. Mp 123−126 °C.

*Thymidine epoxides **15** and **16**.* To a solution of **13** or **14** (0.50 g, 0.86 mmol) in dry acetone (5 mL) under argon was added triethylamine (0.240 mL, 1.72 mmol) at room temperature. The mixture was shaken and left standing for 3 h to allow triethylamine hydrobromide precipitation. After this time, the supernatant was transferred into another flask under inert atmosphere through a membrane filter (0.45 μm GHP ACRODISK 13). The remaining precipitate was washed once with dry acetone (1.5 mL), and filtering was repeated. Then, the solution was evaporated under reduced pressure to afford the epoxides **15** (from **13**) or **16** (from **14**) as white solids, which were immediately subjected to the Grignard addition reaction.

*(1R,6S)-2-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4,6-dimethyl-7-oxa-2,4-diazabicyclo[4.1.0]heptane-3,5-dione (**15**).* ^{1}H NMR (500 MHz, Acetone-d_6, ∼0.5 equiv of TEA) δ 0.09−0.17 (m, 12H), 0.93 (m, 18H), 1.52 (s, 3H), 2.10 (ddd, *J* = 13.2, 6.0, 2.5 Hz, 1H), 2.33 (ddd, *J* = 13.2, 8.5, 6.0 Hz, 1H), 3.10 (s, 3H), 3.77−3.86 (m, 2H), 3.88 (dt, *J* = 3.7, 2.0 Hz 1H), 4.52 (app q, *J* = 3.6 Hz, 1H), 4.98 (s, 1H), 6.33 (dd, *J* = 8.5, 6.0 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (126 MHz, acetone-d_6) δ −5.3, −5.2, −4.6, −4.5, 15.6 (C-8), 16.6, 18.9, 26.2, 26.4, 28.4, 39.8, 55.4, 64.1, 65.3, 73.5, 86.1, 87.9, 151.5, 169.2 ppm. HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{44}N_2O_6Si_2$ [M + Na]$^+$ 523.2630, found 523.2621.

*(1S,6R)-2-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-4,6-dimethyl-7-oxa-2,4-diazabicyclo[4.1.0]heptane-3,5-dione (**16**).* ^{1}H NMR (300 MHz, Acetone-d_6, ∼1 equiv of TEA) δ 0.09−0.24 (m, 18H), 0.93 (s, 12H), 1.56 (s, 3H), 2.13 (ddd, *J* = 13.2, 8.5, 6.0 Hz, 1H), 2.18−2.34 (m, 1H), 3.11 (s, 3H), 3.83−3.93 (m, 3H), 4.52 (dt, *J* = 5.4, 2.5 Hz, 1H), 5.02 (s, 1H), 6.30 (dd, *J* = 8.5, 5.8 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (126 MHz, acetone-d_6) δ −5.2, −4.6, −4.5, 15.7, 18.6, 19.0, 26.2, 26.4, 28.3, 40.1, 55.2, 64.2, 64.4, 73.5, 85.9, 87.8), 151.1, 168.7 ppm. HRMS (ESI$^+$) *m*/*z* calcd for $C_{23}H_{44}N_2O_6Si_2$ [M + Na]$^+$ 523.2630, found 523.2615.

*Addition of Phenylmagnesium Bromide to **15** and **16**.* To a freshly prepared solutions of **15** or **16** (0.5 g, 0.86 mmol) in THF (6 mL) under argon were added 3 M solution of phenylmagnesium bromide in diethyl ether (0.34 mL, 1.03 mmol, 1.2 equiv) in one portion. The resulting mixture was stirred at room temperature for 1 h. After 1 h, the reaction was quenched with 1 M HCl (10 mL) and stirring was continued for 5 min. Then the mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4. The solvents were

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J. Org. Chem. 2016, 81, 3848−3859

evaporated under reduced pressure to give the crude products, which were purified by flash column chromatography to afford **17** (0.34 g, 69%, colorless oil, flash column: EtOAc:hexane 1:6, R_f = 0.25) or **18** (0.35 g, 71%, white solid, flash column: EtOAc:hexane 1:5, R_f = 0.30), depending on the starting material. With compound **18** the crystals suitable for X-ray crystallography were grown from *n*-hexane at −20 °C.

*cis-(5S,6R)-1-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-3,5-dimethyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**17**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05−0.07 (m, 12H), 0.88 (s, 9H), 0.92 (s, 9H), 1.59 (s, 3H), 2.00−2.24 (m, 2H), 3.14 (s, 1H, -O*H*), 3.18−3.33 (m, 4H), 3.40 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.73 (ddd, *J* = 5.3, 3.7, 2.0 Hz, 1H), 4.34 (dt, *J* = 5.2, 2.3 Hz, 1H), 4.67 (s, 1H), 6.25 (dd, *J* = 8.3, 5.7 Hz, 1H), 7.02−7.16 (m, 2H), 7.18−7.35 (m, 3H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.6, −4.6, 18.1, 18.6, 25.9, 26.2, 26.4, 28.3, 38.6, 61.0, 63.5, 71.3, 72.7, 86.8, 87.2, 127.6, 128.2, 128.3, 136.5, 152.5, 173.7 ppm; IR (neat): 3455, 2953, 2928, 2857, 1719, 1673, 1463, 1253, 1028, and 831 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{29}H_{50}N_2NaO_6Si_2$ [M + Na]$^+$ 601.3100, found 601.3092.

*cis-(5R,6S)-1-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-3,5-dimethyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**18**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.12 (s, 3H), −0.07 (s, 3H), 0.12 (s, 3H), 0.13 (s, 3H), 0.81 (s, 9H), 0.94 (s, 9H), 1.57 (ddd, *J* = 13.4, 7.7, 6.1 Hz, 1H), 1.61 (s, 3H), 1.66 (ddd, *J* = 13.4, 6.1, 3.6 Hz, 1H), 3.14 (s, 1H, -O*H*), 3.27 (s, 3H), 3.65 (dd, *J* = 10.6, 4.5 Hz, 1H), 3.69−3.78 (m, 2H), 4.10 (dt, *J* = 6.3, 3.6 Hz, 1H), 4.74 (s, 1H), 6.47 (dd, *J* = 7.7, 6.1 Hz, 1H), 7.05−7.14 (m, 2H), 7.27−7.35 (m, 3H) ppm; ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ −5.1, −5.1, −4.8, −4.7, 18.0, 18.7, 25.8, 26.3, 26.4, 28.5, 37.4, 58.9, 63.1, 71.35, 71.41, 84.3, 86.0, 127.7, 128.5, 128.6, 136.0, 152.8, 173.9 ppm; IR (neat): 3453, 2953, 2929, 2857, 1720, 1674, 1463, 1253, 1029, and 833 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for $C_{29}H_{50}N_2NaO_6Si_2$ [M + Na]$^+$ 601.3100, found 601.3086.

*Synthesis of Compound **17** Using PhZnBr.* Phenylzinc bromide was prepared by adding 0.30 mL of 3 M phenylmagnesium bromide (1.0 mmol) in THF into a solution of 248 mg of zinc bromide (1.1 mmol) dissolved in 2 mL of THF. In a separate flask, freshly prepared epoxide **15** (0.86 mmol) was dissolved in 3 mL THF. The previously prepared zinc nucleophile was then transferred via cannula in one portion, and the mixture was stirred at room temperature for 1.5 h. The reaction was quenched by addition of saturated ammonium chloride (10 mL), and the zinc salts were dissolved upon addition of ammonium hydroxide 28% (10 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (EtOAc:hexane 1:6, R_f = 0.25) to afford **17** as colorless oil in 81% yield (^{1}H NMR was identical to that of (5*S*,6*R*)-*cis* **17** prepared above with PhMgBr).

*Synthesis of Compound **17** Using $AlPh_3$.* Triphenylaluminum was prepared by adding 1.05 mL of 3 M phenylmagnesium bromide in Et_2O (3.2 mmol) into a solution of 0.5 M $AlCl_3$ in THF (2.2 mL, 1.1 mmol) and stirred at room temperature for 16 h under argon.[17] In a separate flask, freshly prepared epoxide **15** (0.86 mmol) was dissolved in 3 mL THF. The previously prepared $AlPh_3$ solution was then transferred via cannula in one portion, and the mixture was stirred at room temperature for 1.5 h, whereupon the reaction was quenched by addition of saturated ammonium chloride (3 mL). EtOAc was added (40 mL), and the aluminum salts were dissolved upon addition of 1 M NaOH (10 mL). The organic layer was separated and washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (EtOAc:hexane 1:6, R_f = 0.25) afforded **17** as colorless oil in 74% yield (^{1}H NMR was identical to that of (5*S*,6*R*)-*cis* **17** prepared previously with PhMgBr).

*Synthesis of Compounds **19**−**22** Using Grignard Reagents.* To a freshly prepared solutions of **15** (0.5 g, 0.86 mmol) in THF (6 mL) under argon was added organometallic reagent (1.03 mmol, 1.2 equiv, RMgX, PhZnBr or $AlPh_3$) in one portion. The resulting mixture was stirred at room temperature for 90 min. After this time, the reaction was quenched with sat. NH_4Cl (10 mL) and stirring was continued for 5 min. Then the mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ (20 mL) and brine (20 mL) and dried over Na_2SO_4. The solvents were evaporated under reduced pressure to give the crude products **19**−**22**, which were purified by flash column chromatography.

*cis-(5S,6R)-6-Butyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-3,5-dimethyldihydropyrimidine-2,4(1H,3H)-dione (**19**).* Butylmagnesium chloride (0.65 mL, 2 M solution in THF) as a nucleophile afforded **19** (173 mg, 36%) as colorless oil after flash column chromatography (EtOAc:hexane 1:5, R_f = 0.45). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07−0.08 (m, 12H), 0.81−0.92 (m, 3H), 0.89 (s, 9H), 0.91 (s, 9H), 1,19−1.36 (m, 4H)1.38 (s, 3H), 1.43−1.53 (m, 1H), 1.65−1.75 (m, 1H), 1.98 (ddd, *J* = 12.7, 5.6, 2.7 Hz, 1H), 2.05−2.18 (m, 1H), 3.18 (s, 3H), 3.50 (s, 1H, -O*H*), 3.53 (t, *J* = 5.3 Hz, 1H), 3.62−3.74 (m, 2H), 3.82−3.86 (m, 1H), 4.26−4.47 (m, 1H), 6.10 (dd, *J* = 8.3, 5.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, 5.2, −4.6, −4.5, 14.1, 18.1, 18.6, 23.2, 25.9, 25.9, 26.2, 28.0, 28.6, 31.3, 38.9, 57.6, 63.6, 71.4, 72.3, 86.9, 86.9, 151.9, 175.2 ppm; IR (neat): 3438, 2954, 2928, 2857, 1717, 1463, 1253, 1079, and 831 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{27}H_{54}N_2NaO_6Si_2$ [M + Na]$^+$ 581.3413, found 581.3422.

*cis-(5S,6R)-1-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-6-isopropyl-3,5-dimethyldihydropyrimidine-2,4(1H,3H)-dione (**20**).* Isopropylmagnesium chloride (0.65 mL, 2 M solution in diethyl ether) as a nucleophile afforded **20** (258 mg, 55%) as colorless oil after flash column chromatography (EtOAc:hexane 1:5, R_f = 0.45). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (m, 12H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.90 (s, 9H), 0.97 (d, *J* = 7.0 Hz, 3H), 1.41 (s, 3H), 1.96−2.20 (m, 2H), 2.21−2.38 (m, 1H), 3.15 (s, 3H), 3.43 (d, *J* = 3.8 Hz, 1H), 3.54 (s, 1H, -O*H*), 3.70 (dd, *J* = 4.6 and 2.3 Hz, 2H), 3.83 (td, *J* = 4.3 and 3.1 Hz, 1H), 4.37 (dt, *J* = 6.2 and 3.1 Hz, 1H), 5.81 (dd, *J* = 7.6, 5.9 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.6, −4.5, 18.1, 18.6, 18.8, 21.3, 25.9, 26.2, 26,9, 27.8, 29.8, 39.4, 63.5, 63.6, 71.1, 72.2, 87.0, 88.9, 151.9, 175.3 ppm; IR (neat): 3448, 2955, 2929, 2857, 1717, 1471, 1253, 1079, and 832 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{26}H_{52}N_2NaO_6Si_2$ [M + Na]$^+$ 567.3256, found 567.3281.

*cis-(5S,6S)-1-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-3,5-dimethyl-6-(thiophen-2-yl)dihydropyrimidine-2,4(1H,3H)-dione (**21**).* 2-Thienylmagnesium bromide (1.3 mL, 1 M solution in THF) as a nucleophile afforded **21** (354 mg, 71%) as colorless oil after flash column chromatography (EtOAc:hexane 1:6, R_f = 0.25). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05−0.09 (m, 12H), 0.88 (s, 9H), 0.92 (s, 9H), 1.54 (s, 3H), 2.09−2.18 (m, 2H), 3.22 (s, 3H), 3.37 (s, 1H, -O*H*), 3.45−3.64 (m, 2H), 3.81 (dt, J = 5.9, 3.0 Hz, 1H), 4.36 (dt, *J* = 5.3, 2.6 Hz, 1H), 4.98 (s, 1H), 6.19 (dd, *J* = 7.8, 5.7 Hz, 1H) 6.81−6.89 (m, 2H), 7.19 (dd, *J* = 4.9, 1.4 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.1, −4.7, −4.5, 18.1, 18.6, 25.2), 25.9, 26.2, 28.2, 38.5, 57.1, 63.4, 71.5, 72.3, 86.6, 87.3, 125.7, 126.5, 126.6, 139.5, 151.9, 173.7 ppm. HRMS (ESI$^+$) *m*/*z* calcd for $C_{27}H_{48}N_2O_6SSi_2$ [M + Na]$^+$ 607.2664, found 607.2673.

*cis-(5S,6R)-1-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-ethynyl-5-hydroxy-3,5-dimethyldihydropyrimidine-2,4(1H,3H)-dione (**22**).* Ethynylmagnesium bromide (2.6 mL, 0.5 M solution in THF) as a nucleophile afforded **22** (272 mg, 60%) as white solid after flash column chromatography (EtOAc:hexane 1:5, R_f = 0.30). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06−0.011 (m, 12H), 0.88 (s, 9H), 0.92 (s, 9H), 1.39 (s, 3H), 1.98−2.04 (m, 2H), 2.28 (d, *J* = 2.1 Hz, 1H), 3.23 (s, 3H), 3.54 (broad s, 1H, -O*H*), 3.75 (app t, *J* = 3.3 Hz, 2H), 3.92 (td, *J* = 3.3, 2.1 Hz, 1H), 4.32−4.38 (m, 1H), 4.44 (d, *J* = 2.1 Hz, 1H), 6.18−6.36 (m, 1H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.4, −5.2, −4.7, −4.6, 18.1, 18.7, 23.3, 25.9, 26.2, 28.4, 39.5, 49.0, 63.4, 71.2, 72.4, 73.2, 73.2, 79.3, 85.6, 87.4, 151.9, 173.5 ppm; IR (neat): 3438, 3313, 2954, 2928, 2858, 1672, 1463, 1253, 1112, and 832 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{25}H_{46}N_2NaO_6Si_2$ [M + Na]$^+$ 549.2787, found 549.2806.

N-benzylation of O,O-TBS-thymidine. To a solution of *O*,*O*-TBS-thymidine (1 g, 2.12 mmol) in DMF (10 mL) under argon were added

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J. Org. Chem. 2016, 81, 3848−3859

K_2CO_3 (0.41 g, 3 mmol) and benzyl bromide (0.27 mL, 2.3 mmol), and the resulting mixture was stirred at rt for 14 h, whereupon water (3 mL) was added and stirred for 1 h. Then water (30 mL) and Et_2O (60 mL) were added, and the organic phase was separated, washed with water (1 × 20 mL) and brine (20 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (EtOAc:Hex 1:6, R_f = 0.50) to afford *N*-Bn-*O*,*O*-TBS-thymidine as a colorless oil (1.03 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07−0.11 (m, 12H), 0.89 (s, 9H), 0.92 (s, 9H), 1.94 (d, J = 1.1 Hz, 3H), 1.95−2.04 (m, 1H), 2.25 (ddd, J = 13.1, 5.8, and 2.6 Hz, 1H), 4.04−3.60 (m, 3H), 4.39 (dt, J = 5.5, 2.5 Hz, 1H), 5.14 (app q, 2H), 6.38 (dd, J = 7.9 and 5.8 Hz, 1H), 7.21−7.32 (m, 3H,), 7.45−7.49 (m, 3H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.7, −4.5, 13.4, 18.1, 18.5, 25.9, 26.1, 41.4, 44.6, 63.1, 72.4, 85.6, 87.9, 110.2, 127.6, 128.5, 129.3, 133.7, 137.1, 151.1, 163.6 ppm.

*(5R,6R)-3-Benzyl-5-bromo-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**23**).* To a solution of *N*-Bn-*O*,*O*-TBS-thymidine (1.0 g, 1.8 mmol) in THF (12 mL) was added water (1.2 mL) followed by the addition *N*-bromosuccinimide (1.3 g, 7.2 mmol). The resulting solution was stirred at room temperature for 45 min, whereupon water (10 mL) and Et_2O (40 mL) were added, and the excess bromine was quenched by the addition of solid $Na_2S_2O_5$ in small portions under vigorous stirring until the solution became colorless. The organic phase was separated and washed with water (3 × 10 mL), sat. aq $NaHCO_3$ (10 mL), and brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated under reduced pressure to afford a crude product, which was purified by column chromatography (EtOAc:hexane 1:7, R_f = 0.40) to afford a mixture of diastereomers (dr = 5:1, ^{1}H NMR, 0.97 g, 82%, colorless oil), wherein **23** was the major diasteromer. By collecting first few fractions after further column chromatography (EtOAc:hexane 1:7) gave **23** in 90% diastereomeric pyrity (0.15 g), which was used for the next step. The spectroscopic data are reported only for the major diastereomer **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08−0.12 (m, 12H), 0.89 (s, 9H), 0.93 (s, 9H), 2.02 (s, 3H), 2.08−2.34 (m, 2H), 3.65−3.92 (m, 3H), 4.01 (s, 1H, O*H*), 4.40−4.43 (m, 1H), 4.90−5.15 (m, 3H), 6.54 (t, J = 6.9 Hz, 1H), 7.10−7.50 (m, 5H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.4, −5.3, −4.7, −4.3, 18.1, 18.7, 23.8, 25.9, 26.2, 38.6, 45.0, 53.8, 62.2, 71.0, 80.0, 85.3, 86.1, 127.3, 127.9, 128.5, 137.0, 151.6, 167.1 ppm. HRMS (ESI$^+$) m/z calcd for $C_{29}H_{49}BrN_2NaO_6Si_2$ [M + Na]$^+$ 679.2205, found 679.2226.

*cis-(5S,6R)-3-Benzyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**24**).* To a solution of **23** (0.15 g, 0.23 mmol, 90% diastereomeric purity) in dry acetone (3 mL) under argon was added triethylamine (0.063 mL, 0.45 mmol) at room temperature. The mixture was shaken and left standing for 3 h to allow triethylamine hydrobromide precipitation. After this time, the supernatant was transferred into another flask under inert atmosphere through a membrane filter (0.45 μm GHP ACRODISK 13). The remaining precipitate was washed twice with dry acetone (1.0 mL), and filtering was repeated. The solution was evaporated under reduced pressure, and the resulting white solid residue was dissolved in THF (3 mL). Then a solution of PhZnBr (0.23 mmol) in Et_2O-THF (prepared from 3.0 M PhMgBr in Et_2O and 0.5 M $ZnBr_2$ in THF, rt, 1h) was added, and the solution stirred for 1 h. The reaction was quenched with NH_4Cl (2 mL), and the zinc salts were dissolved upon addition of ammonium hydroxide 28% (10 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic layers were washed with sat. aq $NaHCO_3$ (10 mL) and brine (10 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (EtOAc-Hex 1:5, R_f = 0.30) to afford **24** as colorless oil (0.108 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03−0.05 (m, 12H), 0.86 (s, 9H), 0.91 (s, 9H), 1.58 (s, 3H), 2.03−2.16 (m, 2H), 3.11 (s, 1H, -O*H*), 3.22 (dd, J = 10.9 and 5.1 Hz, 1H), 3.35 (dd, J = 10.9 and 3.6 Hz, 1H), 3.60−3.77 (m, 1H), 4.31 (m, 1H), 4.62 (s, 1H), 3.99 (m, 2H), 6.27 (dd, J = 8.1, 5.9 Hz, 1H), 6.80−6.89 (m, 2H), 6.98−7.09 (m, 2H), 7.09−7.18 (m, 2H), 7.28−7.33 (m, 3H), 7.30−7.45(m, 2H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.6, −4.6, 18.1, 18.6, 25.9, 26.2, 26.2, 38.5, 45.0, 60.7, 63.5, 71.2, 72.8, 86.7, 87.3, 127.7, 128.0, 128.6, 129.8, 136.1, 136.5, 152.0, 173.5 ppm; IR (neat): 3438, 3225, 2954, 2929, 2856, 1672, 1463, 1253, 1108, 1028, and 831 cm^{-1} HRMS (ESI$^+$) m/z calcd for $C_{35}H_{54}N_2NaO_6Si_2$ [M + Na]$^+$ 677.3413, found 677.3432. Mp 101−104 °C.

N-Benzoylation of O,O-TBS-thymidine. To a solution of *O*,*O*-TBS-thymidine (1 g, 2.12 mmol) in MeCN (10 mL) under argon were added TEA (0.59 mL, 4.22 mmol), pyridine (0.17 mL, 2.12 mmol), and benzoyl chloride (0.27 mL, 2.3 mmol). The resulting slurry was heated at 80 °C for 1 h with vigorous stirring. Then water (1 mL) was added and stirring continued while the mixture was cooled down to room temperature. Two M NaOH (15 mL) and Et_2O (70 mL) were added and stirred until all the solids were dissolved. The organic phase was separated, washed with 2 M HCl (2 × 10 mL), 1 M NaOH (15 mL), and brine (15 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude *N*-Bz-*O*,*O*-TBS-thymidine as light brown solid (1.2 g, 98%), which was used in the next step without further purification.^{1}H NMR (300 MHz, $CDCl_3$) δ −0.07−0.14 (m, 12H), 0.88 (s, 9H), 0.95 (s, 9H), 1.96 (d, J = 1.2 Hz, 3H), 1.98−2.11 (m, 1H), 2.28 (ddd, J = 13.0, 5.7, 2.5 Hz, 1H), 3.57−4.12 (m, 3H), 4.23−4.53 (m, 1H), 6.33 (dd, J = 8.0, 5.7 Hz, 1H), 7.32−7.78 (m, 3H,), 7.91−7.94 (m, 2H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.7, −4.5, 12.7, 18.1, 18.6, 25.8, 26.1, 41.6, 63.3, 72.5, 85.3, 88.2, 111.0, 129.2, 130.6, 131.9, 135.0, 149.5, 163.0, 169.1 ppm.

*Synthesis of Thymidine trans-Bromohydrins **26** and **27**.* To a solution of *N*-Bz-*O*,*O*-TBS-thymidine (1.0 g, 1.74 mmol) in THF (12 mL) was added water (1.2 mL) followed by the addition *N*-bromosuccinimide (1.26 g, 7.0 mmol). The resulting solution was stirred vigorously at room temperature for 40 min, whereupon water (10 mL) and Et_2O (50 mL) were added, and the excess bromine was quenched by the addition of solid $Na_2S_2O_5$ in small portions under vigorous stirring until the solution became colorless. The organic phase was separated and washed with water (3 × 10 mL), sat. aq $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4. The solvents were evaporated under reduced pressure to give a crude mixture of diastereomers (dr = 4:1, ^{1}H NMR), which was purified by column chromatography (EtOAc:hexane 1:4, R_f = 0.40) to afford a mixture of diastereomers (dr 5:1, ^{1}H NMR, 0.51 g, 45%), wherein **26** was the major diasteromer.

*trans-(5R,6R)-3-Benzoyl-5-bromo-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-tetrahydrofuran-2-yl)-6-hydroxy-5-methyldihydropyrimidine-2,4-(1H,3H)-dione (**26**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10−0.15 (m, 12H), 0.89 (s, 9H), 0.96 (s, 9H), 2.06 (s, 3H), 2.16−2.34 (m, 2H), 3.75−3.91 (m, 3H), 4.28 (d, J = 2.3 Hz, 1H, O*H*), 4.40−4.48 (m, 1H), 5.21 (d, J = 2.3 Hz, 1H), 6.48 (t, J = 6.8 Hz, 1H), 7.45−7.64 (m, 3H), 8.01−8.03 (m, 2H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.7, −4.3, 18.1, 18.7, 23.1, 25.9, 26.2, 38.7, 53.8, 62.2, 71.1, 80.8, 87.3, 87.8, 129.2, 130.6, 132.2, 150.1, 166.0, 168.0 ppm; HRMS (ESI$^+$) m/z calcd for $C_{29}H_{47}BrN_2NaO_7Si_2$ [M + Na]$^+$ 693.1997, found 693.2021.

*trans-(5S,6S)-3-Benzoyl-5-bromo-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)-tetrahydrofuran-2-yl)-6-hydroxy-5-methyldihydropyrimidine-2,4-(1H,3H)-dione (**27**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06−0.15 (m, 12H), 0.87 (s, 9H), 0.95 (s, 9H), 2.01 (s, 3H), 2.30−2.40 (m, 2H), 3.75−3.96 (m, 3H), 4.35−4.40 (m, 1H), 4.77 (d, J = 5.0 Hz, 1H, O*H*), 5.57 (d, J = 5.0 Hz, 1H), 5.88 (t, J = 6.8 Hz, 1H), 7.45−7.64 (m, 3H), 8.01−8.03 (m, 2H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.7, −4.3, 18.1, 18.7, 23.1, 25.9, 26.2, 41.9, 53.8, 63.6, 71.6, 80.1, 85.3, 86.1, 129.2, 130.4, 132.6, 149.0, 163.3, 168.6 ppm; HRMS (ESI$^+$) m/z calcd for $C_{29}H_{47}BrN_2NaO_7Si_2$ [M + Na]$^+$ 693.1997, found 693.2021.

*Synthesis of **28** and **29**.* To a solution of a mixture of **26** and **27** (dr = 5:1, 0.25 g, 0.37 mmol) in dry acetone (5 mL) under argon was added triethylamine (0.068 mL, 0.49 mmol) at room temperature. The mixture was gently shaken and left standing (with no further shaking!) for 1 h to allow triethylamine hydrobromide precipitation as transparent needles. Then the supernatant was transferred into another flask under inert

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atmosphere through a membrane filter (0.45 μm GHP ACRODISK 13). The remaining precipitate was washed twice with dry acetone (1.0 mL), and filtering was repeated. The solution was evaporated under reduced pressure to afford the respective epoxides as white foamy solids. Next, the solids were dissolved in dichloromethane (5 mL) and cooled to −60 °C. Freshly prepared solution of triphenylaluminum in THF (0.45 mmol, prepared from 3 M PhMgBr and $AlCl_3$, rt Fourteen h)[17] was added to the solution containing the epoxides in one portion, and the mixture was stirred until warmed up to 0 °C (∼40 min). The reaction was quenched by addition of saturated ammonium chloride (4 mL), Et_2O (50 mL) added, and the aluminum salts were dissolved upon addition of 2 M NaOH (15 mL). The organic layer was separated and washed with sat. aq $NaHCO_3$ (15 mL) and brine (15 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was flash column chromatographed (EtOAc:hexane 1:4) to afford **28** (146 mg, 59%, R_f = 0.25) as white solid and **29** (27 mg, 11%, R_f = 0.32) as colorless oil. Compound **29** could not be fully purified from the byproduct (approximately 85% purity, ^{1}H NMR), presumably thymidine 5,6-glycol (see NMR spectra on Supporting Information), which formation was due to incomplete reaction or presence of water during the reaction.

*cis-(5S,6R)-3-Benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**28**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03−0.11 (m, 12H), 0.85 (s, 9H), 0.95 (s, 9H), 1.85 (s, 3H), 2.12−2.26 (m, 2H), 2.98 (s, 1H, -O*H*), 3.38 (dd, *J* = 11.0 and 4.6 Hz, 1H), 3.43−3.53 (m, 1H), 3.74−3.78 (m, 1H), 4.33−4.38 (m, 1H), 4.80 (s, 1H), 6.17−6.20 (m, 1H), 7.28−7.44 (m, 5H), 7.48−7.51 (m, 2H), 7.63−7.66 (m, 1H), 7.90−7.92 (m, 2H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.1, −4.7, −4.6, 18.1, 18.6, 25.8, 25.9, 26.2, 38.9, 61.8, 63.6, 71.9, 72.7, 86.9, 87.5, 127.8, 128.5, 129.2, 130.4, 132.6, 135.0, 135.7, 150.7, 169.0, 172.9 (C-4) ppm; IR (neat): 3448, 2955, 2929, 2857, 1672, 1463, 1250, 1109, and 831 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{35}H_{52}N_2NaO_7Si_2$ [M + Na]$^+$ 691.3205, found 691.3221. Mp 91−95 °C.

*cis-(5R,6S)-3-Benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**29**).* ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.12 (s, 6H), −0.07 (s, 6H), 0.80 (s, 9H), 0.97 (s, 9H), 1.61−1.78 (m, 2H),1.88 (s, 3H), 2.93 (s, 1H, -O*H*), 3.62−3.77 (m, 3H), 4.12−4.16 (m, 1H), 4.87 (s, 1H), 6.43−6.48 (m, 1H), 7.36−7.45 (m, 5H), 7.47−7.52 (m, 2H), 7.62−7.68 (m, 1H), 7.89−7.92 (m, 2H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.0, −4.8, −4.7, 18.0, 18.8, 25.8, 25.8, 26.3, 36.7, 59.7, 63.0, 71.1, 72.0, 83.9, 86.2, 127.9, 128.9, 129.2, 130.4, 132.7, 135.0, 135.2, 151.1, 169.2, 173.0 ppm; HRMS (ESI$^+$) *m*/*z* calcd for $C_{35}H_{52}N_2NaO_7Si_2$ [M + Na]$^+$ 691.3205, found 691.3193.

*Synthesis of **28** Using BPh_3.* To a solution of **26** (0.10 g, 0.15 mmol, 90% diastereomeric purity, ^{1}H NMR) in dry acetone (3 mL) under argon was added triethylamine (0.025 mL, 0.18 mmol) at room temperature. The mixture was gently shaken and left standing (with no further shaking!) for 1 h to allow triethylamine hydrobromide precipitation as transparent needles. Then, the supernatant was transferred into another flask under inert atmosphere through a membrane filter (0.45 μm GHP ACRODISK 13). The remaining precipitate was washed twice with dry acetone (0.5 mL), and filtering was repeated. The solution was evaporated under reduced pressure to afford the respective epoxide as white foamy solid. Next, the epoxide was dissolved in THF (3 mL), BPh_3 (44 mg, 0.28 mmol) was added, and the solution was stirred at rt for 1h. The reaction was quenched with sat. aq $NaHCO_3$ (7 mL) and stirred for 10 min. Et_2O (30 mL) was added, and the organic layer was separated and washed with sat. aq $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL). The solution was dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by flash column chromatography (EtOAc:hexane 1:4 (v/v), R_f = 0.25) to afford **28** as a white solid (74 mg, 82%). ^{1}H NMR spectrum was identical to that of **28** prepared using $AlPh_3$.

*cis-(5S,6R)-1-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**25**).* To a solution of **28** (50 mg, 0.075 mmol) in $CHCl_3$ (1 mL), 18.5 μL *n*-octylamine (0.11 mmol, 1.5 equiv) was added and stirred at room temperature for 1 h. Then the solvent was evaporated in vacuo, and the resulting crude mixture flash column chromatographed through silica gel (EtOAc:hexane 1:4, R_f = 0.12) to afford **25** as a white powder (41 mg, 97%). Crystals suitable for X-ray crystallography were grown from a mixture of *i*-PrOH-H_2O. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04−0.07 (m, 12H), 0.87 (s, 9H), 0.92 (s, 9H), 1.65 (s, 3H), 1.89−2.32 (m, 2H), 2.95 (broad s, 1H, -O*H*), 3.24 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.38 (dd, *J* = 11.0, 3.7 Hz, 1H), 3.72 (ddd, *J* = 5.4, 3.6, 1.9 Hz, 1H), 4.33 (dt, *J* = 5.5, 2.1 Hz, 1H), 4.67 (s, 1H), 6.20 (dd, *J* = 8.4, 5.6 Hz, 1H), 7.20−7.20 (m, 5H), 7.81 (broad s, 1H, -N*H*) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.2, −4.6, −4.6, 18.2, 18.6, 25.9, 26.20, 26.27, 38.6, 62.2, 63.5, 71.6, 72.7, 86.3, 87.3, 127.7, 128.36, 136.09, 151.4, 173.3 ppm; IR (neat): 3217, 2955, 2929, 2858, 1672, 1253, 1094, 1028, 835, and 774 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{28}H_{48}N_2NaO_6Si_2$ [M + Na]$^+$ 587.2943, found 587.2936.

*(4R,5S)-Methyl 3-((2R,4S,5R)-4-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-2-oxo-4-phenyloxazolidine-5-carboxylate (**30**).* To a solution of **28** (30 mg, 0.044 mmol) in MeOH (1 mL), 89.6 μL of 0.5 M KOH in MeOH (0.044 mmol, 1.0 equiv) was added and stirred at room temperature for 20 min, whereupon water (4 mL) and EtOAc (15 mL) were added. The organic layer was separated, washed once with water (5 mL) and brine (5 mL), and dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give the crude product, which was purified by column chromatography (EtOAc:hexane 1:4, R_f = 0.50) affording **30** as a colorless oil (14 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.05 (m, 6H), 0.01 (s, 3H), 0.02 (s, 3H) 0.83 (s, 9H), 0.84 (s, 9H), 1.09 (s, 3H), 1.89 (ddd, *J* = 12.8, 5.6, 2.1 Hz, 1H), 2.29 (ddd, *J* = 13.1, 8.9, 5.3 Hz, 1H), 2.63 (dd, *J* = 10.6, 8.6 Hz, 1H), 3.05 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.48−3.74 (m, 1H), 3.86 (s, 3H), 4.19−4.22 (m, 1H), 5.07 (s, 1H), 5.61 (dd, *J* = 8.8, 5.6 Hz, 1H), 7.24−7.27 (m, 1H), 7.37−7.40 (m, 4H) ppm; ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ −5.3, −5.3, −4.7, −4.6, 18.1, 18.5, 20.2, 25.9, 26.1, 36.3, 53.5, 63.4, 65.0, 73.0, 82.2, 85.0, 86.8, 128.4, 128.7, 129.2, 135.2, 155.8, 172.8 ppm. IR (neat): 2955, 2929, 2857, 1772, 1258, 1028, 833, and 744 cm^{-1}. HRMS (ESI$^+$) *m*/*z* calcd for $C_{29}H_{49}NO_7Si_2$ [M + Na]$^+$ 602.2940, found 602.2936.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00495.

Crystallographic data for (CCDC-934918 (**3**), CCDC-934919 (**9**), CCDC-1004127 (**18**), and CCDC-1448807 (**25**) (CIF)

DFT results and copies of NMR spectra for all new compounds. X-ray crystallographic data of compounds **3**, **9**, **18**, and **25**. Crystallographic data contains the supplementary crystallographic data and can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif) (PDF)

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Notes

The authors declare no competing financial interest.

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