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FULL PAPER

Syntheses of C6 Aryl and Alkynyl Thymidines from Thymidine *trans*-5,6-Bromohydrins

Pauli Wrigstedt, Vladimir Iashin, Kalle Lagerblom, Juha Keskiväli, Konstantin Chernichenko and Timo Repo*

Abstract: C6-substituted thymidines are biochemically important compounds, whereas thymidine (6-4) photoproduct (5-hydroxy-6-(thymidine-4-yl) dihydrothymidine) is one of the major DNA damage caused by the UV component of sunlight. This report describes a metal-free *cis*-diastereoselective ring opening of thymidine 5,6-epoxides using mildly nucleophilic organofluoroborates in the presence of $BF_3{\cdot}Et_2O$, providing a facile access to (6-4) photoproduct analogues. A broad range of aryl and alkynylfluoroborates are compatible with the reaction that also tolerates various protecting groups. Furthermore, the epoxide addition products undergo thionyl chloride-pyridine promoted dehydration to the respective pharmaceutically attractive C6-substituted thymidines in high yields, thus providing a new and straightforward method for their synthesis.

Introduction

Thymine nucleobase and nucleoside analogues are extensively explored for antimicrobial activity,[1] treatment of cancer,[2] as antiviral agents,[3] and in studies of DNA repair[4] and strand breaking.[5] Many of the synthetic bioactive pyrimidines possess a C6 alkyl or aryl core. Illustrative examples are the HIV-active non-nucleoside transcriptase inhibitors (NNRTIs) emivirine[6] and SJ-3366[7] (Figure 1). Although these compounds and their analogues are structurally rather simple, their syntheses typically require an extensive chemical work.[8]

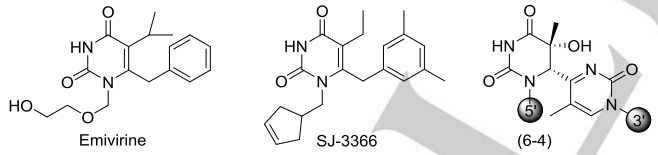
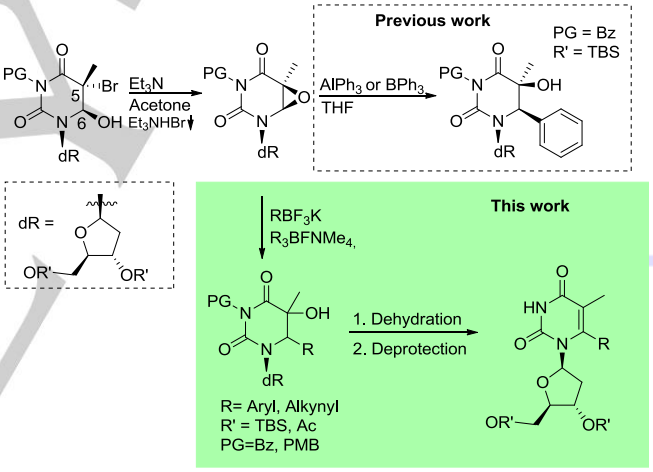


Figure 1. Examples of bioactive thymine analogues and thymidine (6-4) photoproduct.

Existing synthetic approaches to C6-functionalized thymines involve cycloaddition of ketoesters with thiourea,[9] reactions through trichloropyrimidines,[10] or lithiation and subsequent treatment with electrophiles such as aromatic aldehydes.[11] Additionally, the latter method allows for the preparation of 6-iodothymine, which undergoes palladium-catalyzed Sonogashira cross-coupling.[12] By contrast, modified thymidine nucleosides (thymine+deoxyribose) are typically prepared in several steps involving the separate modification of the thymine base and the deoxyribose moiety, which are assembled together using various glycosylation methods.[13] The direct incorporation of carbon moiety into the thymidine at the C6 position will be advantageous in reducing the synthetic steps and avoiding the formation of undesired N3-deoxyribose[14] and α-anomer[13] resulting from the glycosylation step.



Scheme 1. Strategy towards C6 aryl and alkynyl thymidines.

Thymidine (6-4) photoproduct is one of the major DNA damage triggered by UV irradiation of genomic DNA. This lesion distorts the DNA helical structure and interferes with DNA replication and transcription which may lead to mutation and cell death (Figure 1).[15] We recently developed a synthetic methodology to access (6-4) photoproduct analogues from readily available thymidine *trans*-5,6-bromohydrins through epoxidation and subsequent ring-opening using various organometallic nucleophiles.[16] However, with an easily removable N3-Benzoyl (Bz) protecting group, the reaction scope was limited to BPh_3 and $AlPh_3$, and did not tolerate other nucleophiles, such as organozinc, organomagnesium or $AlMe_3$ reagents (Scheme 1). This was ascribed to the electron-withdrawing Bz group which decreased the reactivity of the epoxide and rendered the dihydropyrimidine N3-C4 bond susceptible to cleaving by strong nucleophiles. Therefore, organozinc reagents were not reactive, while the use

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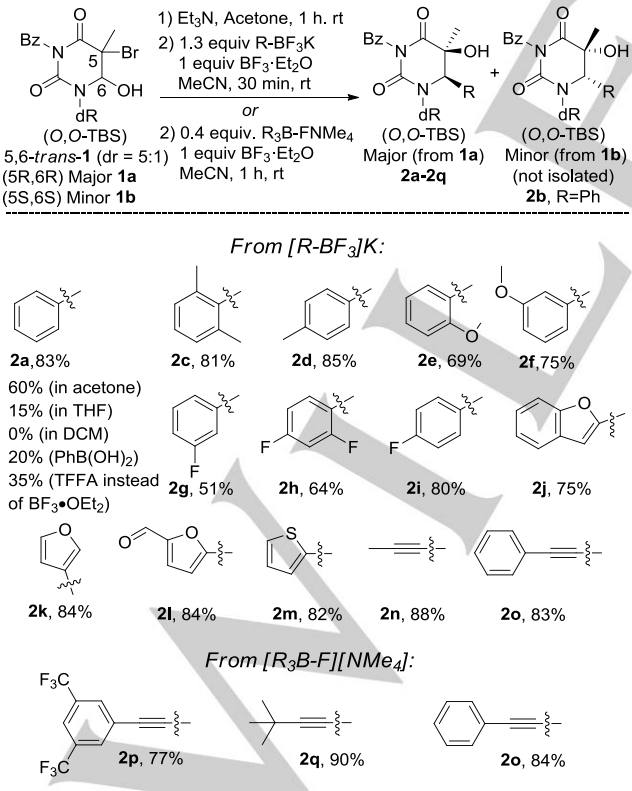
of organomagnesium nucleophiles resulted in decomposition products. Owing to the biological significance of thymidine (6-4) photoproducts, a straightforward access to their analogues is of importance since they can be useful in drug development, such as anticancer and antiviral agents,[3c, 17] in mechanistic studies of DNA repair[4, 17e, 18] and strand breaking, [5] and in the construction of thymidine fluoro- and chromophores.[19]

Herein, we report a *cis*-diastereoselective coupling of various thymidine epoxides with mildly nucleophilic aryl- and alkynylfluoroborate salts. Furthermore, we show that the products can be converted to C6-substituted thymidines through thionyl chloride-pyridine induced dehydration (Scheme 1).

Results and Discussion

Potassium organotrifluoroborates are a new class of commercially available air-stable, low toxic and mildly nucleophilic boronic acid derivatives that are important reagents for a vast array of chemical transformations,[20] such as Suzuki-Miyaura cross-coupling,[21] allylation and crotylation of aldehydes and ketones,[22] and ring-opening of benzylic epoxides.[23] In our previous work, we demonstrated that *N*-Bz-*O*,*O*-TBS thymidine epoxide undergoes *cis* diastereoselective C6-phenylation in the presence of BPh_3 (Scheme 1, TBS = *tert*-butyldimethylsilyl).[16] On this basis, we hypothesized that potassium organotrifluoroborates would behave equivalently when activated with $BF_3{\cdot}OEt_2$.



Scheme 2. The scope of the reaction.

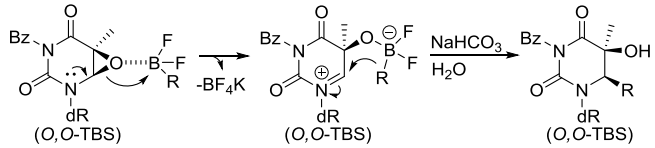
To test our hypothesis, we prepared *trans*-bromohydrin **1** (mixture of **1a** and **1b**, dr = 5:1, Scheme 2) by treating *N*-Bz-*O*,*O*-TBS thymidine with N-bromosuccinimide (NBS) in H_2O-THF.[16] The formation of the epoxides by exposing **1** to triethylamine (1.2 equiv) in acetone and the subsequent addition of potassium phenyltrifluoroborate (1.3 equiv) in acetone, in the presence of $BF_3{\cdot}OEt_2$ (1.0 equiv), afforded the products **2a** and **2b** *cis*-diastereoselectively (**2a** was isolated in 60% yield, no *trans*-products observed). The *cis* diastereochemical arrangement of **2a** (5S, 6R) and **2b** (5R,6S, determined from the crude products) was confirmed by comparing the ^1H and ^{13}C NMR spectra to those of authentic compounds.[16] Screening of solvents (DCM, THF, acetone, MeCN, Scheme 2) identified MeCN as optimal, giving **2a** in 83% isolated yield. Lower yields of 20% and 35% of **2a** were obtained using phenylboronic acid as a nucleophile or trifluoroacetic anhydride (TFAA) as promoter in place of $BF_3{\cdot}OEt_2$, respectively. Interestingly, in the diastereoselective ring opening of benzylic epoxides with potassium alkenyl and phenyltrifluoroborates, TFFA performed notably better than $BF_3{\cdot}OEt_2$.[23]

Once the satisfactory conditions were determined (1.3 equiv of RBF_3K and 1.0 equiv of $BF_3{\cdot}OEt_2$, MeCN, 30 min), we explored the reaction scope with various commercially available aryl and alkynyltrifluoroborate salts. For analytics and determination of the yields, only major diastereomers were isolated (*cis*-products from **1a**, yields calculated accordingly) due to the low amount of minor *cis*-diastereomers (products from **1b**) present in the crude mixtures, except with **2c**, which gave inseparable mixture of *cis*-diastereomers. The reaction performed well with electron-rich aryltrifluoroborates (Ph, *o*- or *m*-OMe and *p*-Me,) even with sterically demanding 2,5-di-Me substituents, affording the products **2a**-**2f** in good yields. Slight decrease in the product yields occurred using aryltrifluoroborates bearing electron-withdrawing fluorine substituents, particularly at *ortho* or *meta* position (**2g**-**2i**). Unfortunately, no reaction occurred using aryltrifluoroborates with strongly electron-withdrawing substituents, such as 3,5-CF_3 or 2-NO_2, or alkyltrifluoroborates (*n*-$BuBF_3K$). Heteroaryl trifluoroborates 2-thienyl, 3-furanyl and 2-benzofuranyl reacted nicely with the epoxide and gave the products **2j**, **2k** and **2m** in good yields. The reaction tolerated aldehydes as the addition of potassium 5-formyl-2-furantrifluoroborate generated the desired product **2l** in a very good 82% yield. Additionally, the method was amenable to potassium propynyl and phenylethynyltrifluoroborates, furnishing C6-alkynyl alcohols **2n** and **2o** in high yields. It should be added that the reaction could also be conducted in one-pot in MeCN by treating **1** with Et_3N for 15 min prior to the addition of RBF_3K and BF3·OEt_2 (no isolation of the epoxide and precipitation of Et_3NHBr). Albeit this resulted in slight decrease in the product yields (68% with **2f** and 72% with **2n**), the procedure was simplified substantially, thereby rendering this approach applicable.

To expand the substrate scope, we investigated the compatibility of the reaction with tetramethylammonium trialkynylfluoroborates, prepared by organometallic-free borylation of alkynes.[24] These alkynyltrifluoroborate surrogates were competent nucleophiles in the allylic substitution of glucals and the synthesis of propargyl

ethers. Three different reagents having both electron-releasing (*tert*-Bu, Ph) and electron-withdrawing (3,5-$(CF_3)_2$Ph) substituents attached to the alkynyl moiety were tested in typical reaction conditions (Scheme 2). Much to our delight, all the prepared reagents coupled efficiently with the epoxide, generated from **1**, and gave the desired products **2p**, **2q** and **2o** in high yields using sub-equimolar amount (0.4 equiv) of the reagents. The electron-rich alkynyls provided the products in higher yields than the electron deficient ones, in decreasing order of *tert*-Bu > Ph > di-CF_3Ph).

The exclusive formation of *cis*-diastereomers indicates that the epoxide opens before the nucleophilic attack (Scheme 3), apparently in a similar manner as the epoxide openings of 2,3-piperidines with organozinc reagents[25] and glycals with organoaluminum compounds.[26]



Scheme 3. Putative mechanism using RBF_3K with $BF_3{\cdot}OEt_2$.

With the small library of C6-modified dihydrothymidine alcohols in hand, we undertook efforts to design an efficient C5-dehydration method to restore the double bond present in thymidine nucleosides, acknowledging the presence of an acid labile glycosidic bond (Table 1).

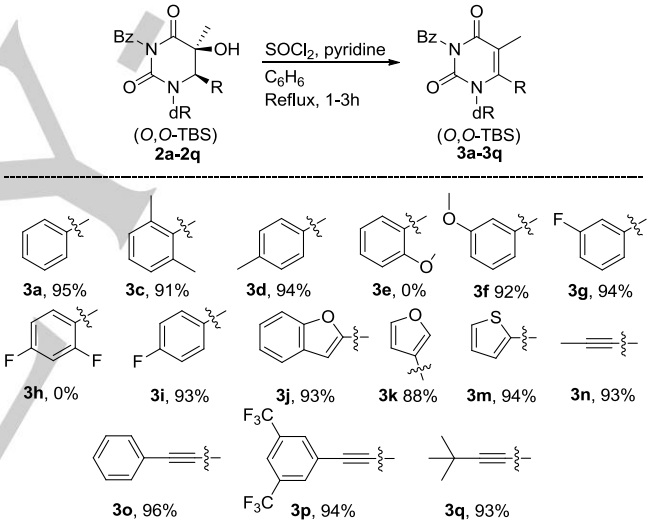
Table 1. Dehydration of **2a** to 6-phenylthymidine **3a**.[a]

Reagents[b]	Base[b]	Solvent[c]	Time (h)	Yield (%)
MsCl-Et_3N[d]	-	$CDCl_3$	30	27
MsCl-Et_3N	Pyridine	$CDCl_3$	30	40[e]
MsCl-Et_3N	DBN	$CDCl_3$	2	44
MsCl-Et_3N	Pyridine	C_6D_6	8	54
MsCl-Et_3N	DBN	C_6D_6	2	43
$SOCl_2$	Pyridine	$CDCl_3$	3	92[e]
SOCl2	Pyridine	C_6D_6	1	95[e]

[a] 10 mg of **2a**, reflux, monitored by ^{1}H NMR [b] 1.1 equiv of MsCl or 1.2 equiv of SOCl2, added at rt. [c] 20 equiv of pyridine, 1.5 equiv of DBN [d] 10 equiv of Et_3N [e] isolated yields.

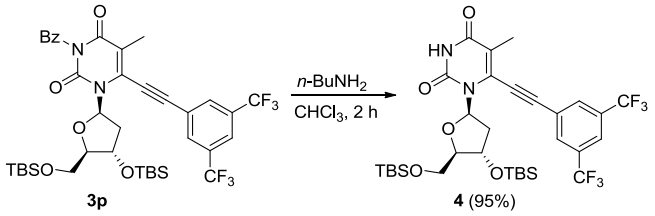
Initially, we attempted the base catalyzed dehydration of **2a** to 6-phenylthymidine **3a** by converting the C5-alcohol to mesylate using MsCl in the presence of various bases (DBN, pyridine and Et_3N).[27] Albeit the mesylation of **2a** occurred smoothly (full conversion in 30 min with 1.1 equiv of MsCl in the presence of 1.5 equiv of Et_3N, ^{1}H NMR), the dehydration upon reflux was sluggish and low yielding, regardless of the base or solvent. Gratifyingly, the utilization of thionyl chloride ($SOCl_2$) with an excess of pyridine[28] in refluxing $CDCl_3$ afforded **3a** in an excellent 92% yield after 3 h. Utilization of toluene accelerated the reaction significantly, but accompanied by inconsistencies in the isolated products, particularly at temperatures over 90 ℃. This was addressed by employing lower-boiling benzene as solvent, which gave **3a** consistently in near quantitative yields in less than 1 h.

The scope of the dehydration was examined with all the prepared dihydrothymidine alcohols **2a**-**2q**, except with **2l** due to the incompatibility of the aldehyde group with $SOCl_2$ (Scheme 4). All the alcohols, with the exception **2e** and **2h**, underwent dehydration furnishing the corresponding C6-thymidines in high yields. The reaction performed equally well with a mixture of diastereomers (**2c**, dr = 4:1), affording **3c** as the sole product in 91% yield. It is worth noting that with **2e** and **2h** we did not observe the dehydrated products even after 14 h of refluxing.



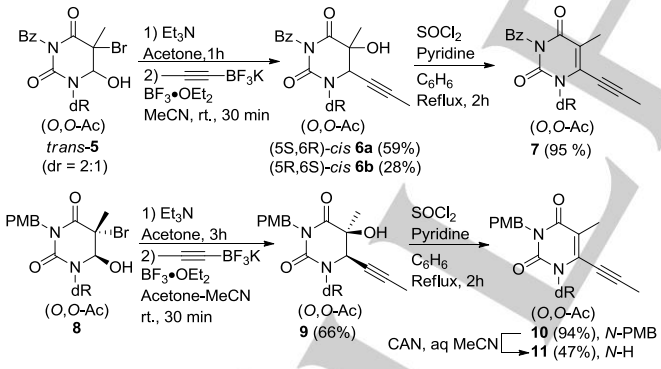
Scheme 4. The scope of the dehydration**.**

The selective N3-debenzoylation of C6-substituted dihydrothymidine alcohols can be achieved using primary alkylamines, such as *n*-$BuNH_2$ and *n*-$OctNH_2$, whereas the use of smaller nucleophiles, such as aqueous NH_3 in MeOH or KOH in MeOH leads to the dihydrothymidine rearrangement to 2-oxazolidinones.[16] As illustrated in Scheme 5, the method was also applicable to C6-substituted thymidines as the treatment of **3p** with *n*-$BuNH_2$ gave the debenzoylated C6-alkynylthymidine **4** in an excellent 95% yield. Due to the highly ^{19}F NMR sensitive CF_3 groups, compound **4** could find application in protein chemistry to monitor various biological processes.[29]



Scheme 5. *N*-debenzoylation of **3p** with *n*-$BuNH_2$.

To evaluate the method using other removable protecting groups at N3 and sugar moiety, we prepared two bromohydrins: *trans N*-Bz-*O*,*O*-Ac **5** (dr = 2:1, mixture of diastereomers) and *N*-PMB-*O*,*O*-Ac **8** (dr = 3:2, major diastereomer, separated by column chromatography, PMB = *p*-methoxybenzyl) using NBS in THF-H_2O (Scheme 6). Both compounds underwent epoxidation when treated with Et_3N in acetone, albeit **8** required longer reaction time which was ascribed to the electron donating nature of the *N*-PMB group. The subsequent addition of potassium propynyltrifluoroborate in the presence of $BF_3{\cdot}OEt_2$ afforded the corresponding 6-propynyl dihydrothymidine *cis*-alcohols **9**, **6a** and **6b** in very good yields. It is noteworthy that the minor diastereomer **6b**, which possess identical configuration (5S,6R) to that of (6-4) photoproduct (Figure 1), could be isolated in a reasonable 28% yield. Both *N*-PMB and *O*,*O*-Ac protecting groups tolerated the dehydration conditions and provided the corresponding C6-propynyl thymidines **7** and **10** in excellent yields. The removal of PMB group from **10** by ceric ammonium nitrate (CAN) in aqueous MeCN[30] afforded the *N*-H-6-propynyl thymidine **11** in 47 % yield.



Scheme 6. Reaction sequence using *N*-PMB and *O*,*O*-Ac protecting groups.

Conclusions

In summary, we have developed a $BF_3{\cdot}Et_2O$-assisted regio- and diastereoselective addition of various aryl- and alkynylfluoroborates to thymidine 5,6-epoxides that offers a complementary and broadened substrate scope compared to current procedures. The presented methodology is compatible with various protecting groups, particularly with easily removable N3-Bz group. Additionally, dehydration of the products using thionyl chloride and pyridine gave the corresponding pharmaceutically relevant C6-substituted thymidines in good overall yields, consequently introducing a new and simple procedure for their synthesis. Both C6-functionalized dihydrothymidine alcohols and their dehydrated counterparts find potential applications in drug development as anticancer and antiviral agents, in the construction of thymidine fluoro- and chromophores and in mechanistic studies of DNA repair and strand breaking.

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 ESI-TOF mass spectrometer. ^1H NMR and ^{13}C NMR spectra were acquired at 27 °C using 300 MHz (300 MHz ^1H-frequency and 75 MHz ^{13}C-frequency) or 500 MHz (500 MHz ^1H-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 ^1H and 77.16 ppm for ^{13}C. Coupling constants are reported in Hz. ^{13}C NMR experiments were performed using APT pulse sequence ($^{13}C\{^1H\}$ 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 NMR spectra were processed with MestReNova 7.1.2.

General procedure for the coupling of 1a with RBF_3K salts (Scheme 2)

1 (diastereomeric mixture of *trans* **1a** and **1b**, dr = 5:1) was prepared using the method described previously.[16] Only coupling products from **1a** (**2a**-**2o**) were isolated and yields calculated accordingly.

To a solution of **1** (0.12 g, 0.18 mmol, mixture of *trans*-diastereomers **1a** (100mg, 0.149 mmol) and **1b** (20 mg), dr = 5:1) in dry acetone (2.5 mL) under argon was added triethylamine (31 µL, 0.22 mmol) at room temperature. The mixture was gently shaken and left standing for 1 h (with no shaking!) to allow triethylamine hydrobromide precipitation as transparent needles. The supernatant was then transferred into another flask under argon using a syringe (Ø 0.6 mm × 25 mm needle). The remaining precipitate was washed with dry acetone (2×0.7 mL) and the combined solvents were evaporated *in vacuo* to afford the mixture of epoxides as a white solid, which was then dissolved in MeCN (2 mL). To this solution, desired amount of RBF_3K (0.23 mmol, 1.3 equiv) was added, followed by the addition of $BF_3{\cdot}OEt_2$ (0.18 mmol, 1 equiv) under argon. The mixture was stirred for 30 min (RBF_3K) and then quenched with sat. aq. $NaHCO_3$ (3 mL) with vigorous stirring for 5 min. EtOAc (30 mL) and water (7 mL) were added, the organic layer separated, washed with brine (1×10 mL), dried over $NaSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography to afford the title products **2a**-**2o**.

(5S,6R)-3-benzoyl-1-(4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyl-6-phenyldihydropyrimidine-2,4(1H,3H)-dione (**2a**).

Potassium phenyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.25) afforded **2a** as colorless oil (82 mg, 83%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.03-0.11 (m, 12H), 0.85 (s, 9H), 0.95 (s, 9H), 1.84 (s, 3H), 2.12 – 2.13 (m, 1H), 2.22 – 2.26 (m, 1H), 2.98 (s, 1H), 3.36-3.40 (m, 1H), 3.47-3.50 (m, 1H), 3.76 (br s, 1H), 4.35-4.36 (m, 1H), 4.80 (s, 1H), 6.17-6.20 (m, 1H), 7.31 – 7.42 (m, 5H), 7.48-7.51 (m, 2H), 7.63-7.66 (m, 1H), 7.90 – 7.92 (m, 2H) ppm; **^{13}C 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, 128.6, 129.2, 130.4, 132.6, 135.0, 135.7, 150.7, 169.0, 172.9 ppm; **HRMS** (ESI^+) *m/z* calcd. for $C_{35}H_{52}N_2NaO_7Si_2$ $[M+Na]^+$ 691.3205, found 691.3194.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(2,6-dimethylphenyl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2c**).

Potassium 2,6-dimethylphenyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.3) afforded **2c** as a mixture of *cis*-diastereomers as colorless oil (102 mg, 81%).

Major diastereomer: **^{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, 168.7, 173.7 ppm. **HRMS** (ESI^+) *m/z* calcd. for $C_{37}H_{56}N_2NaO_7Si_2$ $[M+Na]^+$ 719.3518, found 719.3511.

Minor diastereomer: **^{1}H NMR** (300 MHz, $CDCl_3$) δ-0.08-0.11 (m, 12H), 0.82-0.94 (m, 18H), 1.93-1.95 (m, 4H), 2.35-2.50 (m, 7H), 3.05-3.11 (m, 2H), 3.33-3.41 (m, 1H), 3.65-3.74 (m, 1H), 3.96-3.98 (m, 1H), 5.43 (s, 1H), 6.39-6.44 (m, 1H), 6.99-7.13 (m, 3H), 7.48-7.53 (m, 2H), 7.63-7.68 (m, 1H), 7.93-7.95 (m, 2H) ppm **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ δ -5.2, -4.8, -4.6, 18.5, 21.3, 22.4, 25.8, 26.1, 28.2, 36.3, 58.8, 63.3, 70.5, 71.7, 84.8, 85.9, 128.4, 129.0, 129.3, 130.6, 131.7, 132.2, 132.7, 135.0, 136.4, 139.4, 151.3, 168.7, 173.5 ppm **HRMS** (ESI^+) *m/z* calcd. for $C_{37}H_{56}N_2NaO_7Si_2$ $[M+Na]^+$ 719.3518, found 719.3511.

(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-(p-tolyl)dihydropyrimidine-2,4(1H,3H)-dione (**2d**).

Potassium *p*-tolyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.3) afforded **2d** as a colorless oil (87 mg, 85%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 0.94 (s, 9H), 1.82 (s, 3H), 2.10-2.25 (m, 2H), 2.34 (s, 3H), 2.93 (s, 1H, -*OH*), 3.36-3.52 (m, 2H), 3.74-3.78 (m, 1H), 4.33-4.36 (m, 1H), 4.76 (s, 1H), 6.16 (dd, *J*=8.1, 5.7 Hz, 1H), 7.16-7.30 (m, 4H), 7.46-7.51 (m, 2H), 7.62-7.67 (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, 18.7, 21.3, 25.9, 26.2, 39.0, 61.7, 63.6, 71.9, 72.7, 87.0, 87.5, 127.7, 129.2, 129.4, 130.4, 132.7, 135.0, 138.4 150.7, 169.1, 173.0 ppm;. **HRMS** (ESI^+) *m/z* calcd. for $C_{36}H_{54}N_2NaO_7Si_2$ $[M+Na]^+$ 705.3362, found 705.3340.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-6-(2-methoxyphenyl)-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2e**).

Potassium 2-methoxyphenyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:5, R_f = 0.2) afforded **2e** as a colorless oil (72 mg, 69%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.08 (s, 3H), -0.03 (s, 3H), 0.13 (s, 6H), 0.81 (s, 9H), 0.95 (s, 9H), 1.55-1.65 (m, 2H), 1.88 (s, 3H), 3.01 (s, 1H, -*OH*), 3.55-3.61 (m, 2H), 3.76-3.80 (m, 2H), 3.90 (s, 3H), 4.09-4.13 (m, 1H), 5.29 (s, 1H), 6.43 (dd, *J*=7.9, 6.3 Hz, 1H), 6.85 (dd, *J*=8.2 Hz, 2.2 Hz, 1H), 6.91-6.94 (m, 1H), 6.99-7.04 (m, 1H), 7.30-7.35 (m, 1H), 7.40-7.43 (m, 1H), 7.48-7.53 (m, 2H), 7.62-7.68 (m, 1H), 7.92-7.95 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -4.7, 18.0, 18.6, 25.8, 26.2, 26.4, 36.3, 54.1 (br s, C-6), 56.1, 63.6, 72.0 (C-3' and C-5), 84.4, 86.2, 111.5, 121.8, 124.9, 127.3, 129.2, 130.2, 130.4, 132.7, 135.0, 137.3, 151.4 157.5, 169.4, 173.1 ppm;. **HRMS** (ESI^+) *m/z* calcd. for $C_{36}H_{54}N_2NaO_8Si_2$ $[M+Na]^+$ 721.3311, found 721.3315.

(5S,6R)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-6-(3-methoxyphenyl)-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2f**).

Potassium 3-methoxyphenyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.25) afforded **2f** as a colorless oil (78 mg, 75%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 0.94 (s, 9H), 1.83 (s, 3H), 2.11-2.28 (m, 2H), 2.94 (s, 1H, -*OH*), 3.40-3.54 (m, 2H), 3.76-3.79 (m, 1H), 3.84 (s, 3H), 4.34-4.37 (m, 1H), 4.76 (s, 1H), 6.16 (dd, *J*=8.2, 5.6 Hz, 1H), 6.85 (dd, *J*=8.2 Hz, 2.2 Hz, 1H), 6.97-6.99 (m, 2H), 7.24-7.29 (m, 1H), 7.46-7.52 (m, 2H), 7.62-7.67 (m, 1H), 7.90-7.93 (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, 26.2, 39.0, 55.5, 61.9, 63.6, 71.9, 72.7, 87.0, 87.6, 112.7, 114.6, 120.3, 129.2, 129.5, 130.4, 132.6, 135.0, 137.3, 150.6, 160.0, 169.1, 172.9 ppm;. **HRMS** (ESI^+) *m/z* calcd. for $C_{36}H_{54}N_2NaO_8Si_2$ $[M+Na]^+$ 721.3311, found 721.3312.

(5S,6R)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(3-fluorophenyl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2g**).

Potassium 3-fluorophenyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.35) afforded **2g** as a foamy oil (52 mg, 51%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.04-0.12 (m, 12H), 0.85 (s, 9H), 0.95 (s, 9H), 1.82 (s, 3H), 2.10-2.23 (m, 2H), 3.08 (s, 1H, -*OH*), 3.40-3.55 (m, 2H), 3.75-3.78 (m, 1H), 4.34-4.37 (m, 1H), 4.84 (s, 1H), 6.21-6.25 (m, 1H), 7.02-7.05 (m, 1H), 7.11-7.16 (m, 1H), 7.20-7.23 (m, 1H), 7.31-7.38 (m, 1H), 7.47-7.52 (m, 2H), 7.63-7.68 (m, 1H), 7.88-7.91 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.3, -5.1, -4.7, -4.6, 18.1, 18.7, 25.8, 26.2, 39.2, 60.6, 63.6, 71.7, 72.7, 86.6, 87.7, 115.4 (d, *J* (C,F) = 20.9 Hz), 115.6 (d, *J* (C,F) = 22.6 Hz), 123.0, 129.2, 130.0 (d, *J* (C,F) = 8.1 Hz), 132.6, 135.1, 138.7 (d, *J* (C,F) = 6.8 Hz), 150.5, 162.7 (d, *J* (C,F) = 246 Hz), 168.8, 172.8 ppm; **HRMS** (ESI^+) *m/z* calcd. for $C_{35}H_{51}FN_2NaO_7Si_2$ $[M+Na]^+$ 709.3111, found 709.3093.

(5S,6R)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(2,4-difluorophenyl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2h**).

Potassium 2,4-difluorophenyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:6, R_f = 0.25) afforded **2h** as a colorless oil (67 mg, 64%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.04-0.08 (m, 12H), 0.85 (s, 9H), 0.92 (s, 9H), 1.84 (s, 3H), 2.12-2.16 (m, 2H), 3.18 (s, 1H, -*OH*), 3.38-3.47 (m, 2H), 3.74-3.78 (m, 1H), 4.36 (m, 1H), 5.07 (s, 1H), 6.20-6.24 (m, 1H), 6.76-6.84 (m, 1H), 6.90-6.97 (m, 1H), 7.42-7.54 (m, 3H), 7.65-

7.70 (m, 1H), 7.91-7.93 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.4, -5.2, -4.6, -4.6, 18.1, 18.7, 25.9, 26.1, 26.2, 38.3, 54.6, 63.7, 71.8, 72.9, 86.7, 87.6, 104.0 (t, *J* (C,F) = 26.1 Hz), 112.1 (dd, *J* (C,F) = 21.1, 2.5 Hz), 120.6 (d, *J* (C,F) = 13.5 Hz), 127.9 (m), 129.4, 130.5, 132.4, 135.3, 150.6, 160.3 (dd, *J* (C,F) = 144.3, 10.8 Hz), 163.6 (dd, *J* (C,F) = 154.7, 12.5 Hz), 168.9, 172.7 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{35}H_{50}F_2N_2NaO_7Si_2$ $[M+Na]^+$ 727.3017, found 727.2991.

(5S,6R)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(3-fluorophenyl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2i**).

Potassium 4-fluorophenyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:3.5, R_f = 0.40) afforded **2i** as a foamy oil (82 mg, 80%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.86 (s, 9H), 0.95 (s, 9H), 1.82 (s, 3H), 2.15-2.20 (m, 2H), 3.06 (s, 1H, *-OH*), 3.37-3.53 (m, 2H), 3.77 (m, 1H), 4.34-4.36 (m, 1H), 4.81 (s, 1H), 6.22 (dd, *J*=8.1, 5.8 Hz, 1H), 7.02-7.08 (m, 2H), 7.36-7.41 (m, 2H), 7.47-7.52 (m, 2H), 7.63-7.68 (m, 1H), 7.87-7.90 (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, 26.2, 39.0, 60.7, 63.6, 71.8, 72.6, 86.7, 87.6, 115.4 (d, *J* (C,F) = 21.5 Hz), 129.2, 129.6 (d, *J* (C,F) = 7.9 Hz), 130.4, 131.7, 132.5, 135.1, 150.6, 162.8 (d, *J* (C,F)= 247.3 Hz), 168.9, 172.9 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{35}H_{51}FN_2NaO_7Si_2$ $[M+Na]^+$ 709.3111, found 709.3101.

(5S,6S)-6-(benzofuran-2-yl)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2j**).

Potassium benzofuran-2-trifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.25) afforded **2j** as a colorless oil (79 mg, 75%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.16 (s, 3H), 0.17 (s, 3H), 0.85 (s, 9H), 0.98 (s, 9H), 1.77 (s, 3H), 2.15-2.19 (m, 2H), 3.35 (s, 1H, *-OH*), 3.72 (t, *J*=3.7 Hz, 2H), 3.82-3.85 (m, 1H), 4.37-4.40 (m, 1H), 5.14 (s, 1H), 6.16 (t, *J*=6.7 Hz, 1H), 6.81 (s, 1H), 7.22-7.33 (m, 2H), 7.43-7.50 (m, 3H), 7.56-7.58 (m, 1H), 7.62-7.67 (m, 1H), 8.11-8.13 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.2, -5.0, -4.7, -4.5, 18.1, 18.7, 25.3, 25.8, 26.3, 39.8, 55.5, 63.5, 70.8, 72.4, 86.4, 87.7, 107.2, 111.3, 121.6, 123.4, 124.9, 128.1, 129.1, 130.6, 132.7, 135.0, 150.3, 152.9, 154.7, 168.7, 173.1 ppm;; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{37}H_{52}N_2NaO_8Si_2$ $[M+Na]^+$ 731.3154, found 731.3151.

(5S,6R)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(furan-3-yl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2k**).

Potassium furan-3-trifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.3) afforded **2k** as a colorless oil (82 mg, 84%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.06-0.07 (m, 12H), 0.87 (s, 9H), 0.91 (s, 9H), 1.71 (s, 3H), 2.08-2.20 (m, 2H), 3.37 (s, 1H, *-OH*), 3.60-3.67 (m, 2H), 3.86 (m, 1H), 4.38 (m, 1H), 4.87 (s, 1H), 6.23 (dd, *J*=8.1, 5.6 Hz, 1H), 6.65 (s, 1H), 7.40-7.43 (m, 3H), 7.58-7.61 (m, 2H), 7.69-7.70 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.4, -5.3, -4.7, -4.5, 18.1, 18.6, 24.8, 25.9, 26.2, 39.6, 53.8, 63.5, 72.2, 72.4, 85.8, 87.4, 111.0, 129.1, 130.4, 132.4, 134.9, 141.7, 142.9, 150.5, 168.6, 173.4 ppm;; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{33}H_{50}N_2NaO_8Si_2$ $[M+Na]^+$ 681.2998, found 681.2994.

5-((4S,5S)-1-benzoyl-3-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyl-2,6-dioxohexahydropyrimidin-4-yl)furan-2-carbaldehyde (**2l**).

Potassium 5-formyl-2-furantrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:2.5, R_f = 0.3) afforded **2l** as a colorless oil (86 mg, 84%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.16 (s, 3H), 0.17 (s, 3H), 0.85 (s, 9H), 0.98 (s, 9H), 1.73 (s, 3H), 2.04-2.18 (m, 2H), 3.38 (s, 1H, *-OH*), 3.69 (d, *J*=3.2 Hz, 2H), 3.82-3.84 (m, 1H), 4.35-4.38 (m, 1H), 5.11 (s, 1H), 6.20-6.24 (m, 1H), 6.60 (d, *J*=3.6 Hz, 1H), 7.22 (d, *J*=3.6 Hz, 1H), 7.53-7.58 (m, 2H), 7.64-7.69 (m, 1H), 8.08-8.10 (m, 2H), 9.63 (s, 1H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.3, -5.0, -4.7, -4.5, 18.1, 18.7, 25.4, 25.8, 26.2, 39.7, 54.7, 63.6, 70.8, 72.6, 86.1, 87.9, 112.3, 121.9, 129.4, 130.7, 132.4, 135.2, 150.0, 152.7, 157.0, 168.7, 172.7, 177.2 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{34}H_{50}N_2NaO_9Si_2$ $[M+Na]^+$ 709.2947, found 709.2935.

(5S,6S)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyl-6-(thiophen-2-yl)dihydropyrimidine-2,4(1H,3H)-dione (**2m**).

Potassium thiophene-2-trifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.3) afforded **2m** as a colorless oil (82 mg, 82%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.05-0.09 (m, 12H), 0.86 (s, 9H), 0.92 (s, 9H), 1.75 (s, 3H), 2.13-2.22 (m, 2H), 3.40 (s, 1H, *-OH*), 3.61-3.63 (m, 2H), 3.85 (m, 1H), 4.37-4.40 (m, 1H), 5.13 (s, 1H), 6.18-6.23 (m, 1H), 7.02-7.05 (m, 1H), 7.27 (m, 1H), 7.31 (dd, *J*=5.2, 1.2 Hz, 1H), 7.38-7.43 (m, 2H), 7.57-7.62 (m, 1H), 7.69-7.73 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.4, -5.1, -4.7, -4.5, 18.1, 18.7, 24.9, 25.9, 26.2, 39.8, 57.4, 63.4, 72.2, 72.3, 86.5, 87.5, 126.6, 127.2, 129.1, 130.5, 132.4, 134.9, 138.7, 150.2, 168.6, 173.1 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{33}H_{50}N_2NaO_7SSi_2$ $[M+Na]^+$ 697.2769, found 697.2756.

(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-(prop-1-yn-1-yl)dihydropyrimidine-2,4(1H,3H)-dione (**2n**).

Potassium propynyltrifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.25) afforded **2n** as a colorless oil (83 mg, 88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.06 (m, 6H), 0.013 (m, 6H), 0.86 (s, 9H), 0.95 (s, 9H), 1.56 (s, 3H), 1.94 (d, *J*=2.1 Hz, 3H), 2.00-2.13 (m, 2H), 3.37 (s, 1H, *-OH*), 3.76-3.78 (m, 2H), 3.91-3.93 (m, 1H), 4.36-4.39 (m, 1H), 4.48-4.50 (m, 1H), 6.19 (dd, *J*=7.9, 5.9 Hz, 1H), 7.43-7.49 (m, 2H), 7.60-7.64 (m, 1H), 8.06 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.33, -5.25, -4.7, -4.6, 3.9, 18.1, 18.7, 22.5, 25.8, 26.2, 39.6, 50.2, 63.7, 72.2, 72.5, 74.9, 82.6, 85.3, 87.6, 129.2, 130.7, 132.4, 134.9, 150.3, 168.3, 172.8 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{32}H_{50}N_2NaO_7Si_2$ $[M+Na]^+$ 653.3049, found 653.3059.

(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-(phenylethynyl)dihydropyrimidine-2,4(1H,3H)-dione (**2o**).

Potassium (phenylethynyl)trifluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:5, R_f = 0.25) afforded **2o** as a colorless oil (86 mg, 83%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.07-0.08 (m, 6H), 0.16 (m, 6H), 0.88 (s, 9H), 0.97 (s, 9H), 1.64 (s, 3H), 2.03-2.12 (m, 2H), 3.59 (s, 1H, *-OH*), 3.77-3.88 (m, 2H), 3.95-3.97 (m, 1H), 4.40-4.43 (m, 1H), 4.90 (s, 1H) 6.31 (dd, *J*=7.6, 6.2 Hz, 1H), 7.26-7.37 (m, 2H), 7.60-7.63 (m, 1H), 7.86 (m, 3H), 8.00-8.04 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.3, -4.7, -4.5, 18.1, 18.7, 23.2, 25.8, 26.2, 39.7, 50.0, 63.8, 72.0, 72.6, 82.5, 85.3, 87.8, 88.9, 117.5, 121.1, 122.6, 124.3, 124.7, 128.3, 129.2, 130.5, 131.7, 132.0, 132.2, 132.5, 133.0, 135.2, 150.2, 167.9, 172.6 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{37}H_{52}N_2NaO_7Si_2$ $[M+Na]^+$ 715.3205, found 715.3202.

Synthesis of Tetramethylammonium trialkynylfluoroborates

Tetramethylammonium trialkynylfluoroborates were prepared according to the procedure described previously.[24]

Syntheses of Tetramethylammonium fluorotris(phenylethynyl)borate and Tetramethylammonium tris(3,3-dimethylbut-1-yn-1-yl)fluoroborate

1 equiv of ethynylbenzene or 3,3-dimethylbut-1-yne was mixed with an equimolar amount of 1,2,2,6,6-pentamethylpiperidine in dry C_6H_6. Then 1.33 eq. of $BF_3{\cdot}SMe_2$ in C_6H_6 was added to the solution and the mixture was stirred at room temperature under argon atmosphere for 17 h (ethynylbenzene) and 24 h (3,3-dimethylbut-1-yne). Then the precipitate of pentamethylpiperidinium tetrafluoroborate was removed by filtration, and the corresponding amount of tetramethylammonium fluoride in CH_2Cl_2 was added. The mixture was stirred for 4 h (ethynylbenzene) and 16 h (3,3-dimethylbut-1-yne). The volatiles were then evaporated giving a solid residue that was dried in vacuum, then washed with benzene giving, after drying, both compounds as a crystalline solids.

Tetramethylammonium fluorotris(phenylethynyl)borate. Yield 82%. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ=7.38 (d, ^3J(H,H)=7.2 Hz, 6H), 7.26 (t, ^3J(H,H)=7.2 Hz, 6H), 7.21 (t, ^3J(H,H)=7.2 Hz, 3H), 3.16 (s, 12H); **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 131.6, 128.6, 127.1, 126.2, 107.1 (br), 94.0, 56.4 (t, ^1J(C,N)=3.9 Hz).

Tetramethylammonium tris(3,3-dimethylbut-1-yn-1-yl)fluoroborate. Yield 79%. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 3.35 (s, 12H), 1.17 (s, 27H); **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 101.5 (m), 95.0 (br), 56.9 (t, ^1J(C,N)=3.9 Hz), 32.0, 28.0.

Synthesis of tetramethylammonium tris((3,5-bis(trifluoromethyl)phenyl)ethynyl)fluoroborate

168 mg (0.70 mmol, 1 eq.) of 1-ethynyl-3,5-bis(trifluoromethyl)benzene and 109 mg (0.70 mmol, 1 equiv) of 1,2,2,6,6-pentamethylpiperidine in 4 ml of benzene were mixed with 122 mg (0.94 mmol, 1.33 eq.) of $BF_3{\cdot}SMe_2$ in 2 ml of benzene, and the mixture was stirred for 13 h at room temperature. The produced precipitate was removed by filtration and washed with 4 ml of benzene. The solution of 46.8 mg (0.50 mmol, 0.72 equiv) of tetramethylammonium fluoride in 4 ml of CH_2Cl_2 was added to the filtrate. The resulting mixture was stirred for additional 14 hours. Volatiles were evaporated and the residue was washed with benzene. The filtrate was evaporated, dissolved in 5 ml of CH_2Cl_2, and evaporated to give the product in 56% yield (107 mg). **^{1}H NMR** (500 MHz, CD_2Cl_2) δ=7.91 (s, 6H), 7.73 (s, 3H), 3.29 (s, 12H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ=131.9, 131.9 (q, ^2J(C,F)=33.3 Hz), 128.4 (m), 123.7 (q, ^1J(C,F)=272.7 Hz), 120.5 (hept, ^3J(C,F)=4.6 Hz), 109.8 (br), 91.5, 56.7 (t, ^1J(C,N)=4.0 Hz).

General procedure for the coupling of 1a with [R_3BF][NMe_4] salts (Scheme 2)

To a solution of **1** (0.12 g, 0.18 mmol, mixture of *trans*-diastereomers **1a** (100mg, 0.149 mmol) and **1b** (20 mg), dr = 5:1) in dry acetone (2.5 mL) under argon was added triethylamine (31 µL, 0.22 mmol) at room temperature. The mixture was gently shaken and left standing for 60 minutes (with no shaking!) to allow triethylamine hydrobromide precipitation as transparent needles. The supernatant was then transferred into another flask under argon using a syringe (Ø 0.6 mm × 25 mm needle). The remaining precipitate was washed with dry acetone (2×0.7 mL) and the combined solvent was evaporated *in vacuo* to afford the mixture of epoxides as a white solid, which was then dissolved in MeCN (2mL). To this solution, desired amount of previously prepared [R_3BF][NMe_4] (0.07 mmol, 0.4 equiv) was added, followed by the addition of $BF_3{\cdot}OEt_2$ (0.18 mmol, 22 µL, 1 equiv) under inert atmosphere. The mixture was stirred for 1 h and then quenched with sat. aq. $NaHCO_3$ (3 mL) with vigorous stirring for 5 min. EtOAc (30 mL) and water (10 mL) were added, the organic layer separated and washed once with brine (10 mL), dried over $NaSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography to afford the products **2o**-**2q**.

The coupling of **1** with Tetramethylammonium fluorotris(phenylethynyl)borate produced **2o** in 84% yield. ^{1}H and ^{13}C NMR spectra of the product were identical to those of obtained above using potassium phenylethynyltrifluoroborate.

(5S,6R)-3-benzoyl-6-((3,5-bis(trifluoromethyl)phenyl)ethynyl)-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2p**).

Tetramethylammonium tris((3,5 bis(trifluoromethyl)phenyl)ethynyl) fluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:6, R_f = 0.36) afforded **2p** as a white solid (95 mg, 77%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.07-0.08 (m, 6H), 0.16 (m, 6H), 0.88 (s, 9H), 0.97 (s, 9H), 1.64 (s, 3H), 2.03-2.12 (m, 2H), 3.59 (s, 1H, *-OH*), 3.77-3.88 (m, 2H), 3.95-3.97 (m, 1H), 4.40-4.43 (m, 1H), 4.90 (s, 1H), 6.31 (dd, *J*=7.6, 6.2 Hz, 1H), 7.26-7.37 (m, 2H), 7.60-7.63 (m, 1H), 7.86 (m, 3H), 8.00-8.04 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.3, -4.7, -4.5, 18.1, 18.7, 23.2, 25.8, 26.2, 39.7, 50.0, 63.8, 72.0, 72.6, 82.5, 85.3, 87.8, 88.9, 122.6 (br s), 122.9 (q, *J* (C,F) = 273.1 Hz), 124.3, 128.3, 129.2, 130.5, 131.7, 132.0, 132.2, 132.6, 133.0, 135.2, 150.2, 167.9, 172.6 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{39}H_{50}F_6N_2NaO_7Si_2$ $[M+Na]^+$ 851.2953, found 851.2951**. Mp** 53-58 ℃.

(5S,6R)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(3,3-dimethylbut-1-yn-1-yl)-5-hydroxy-5-methyldihydropyrimidine-2,4(1H,3H)-dione (**2q**).

Tetramethylammonium tris(3,3-dimethylbut-1-yn-1-yl)fluoroborate as a nucleophile. Column chromatography (EtOAc:Hexane 1:6, R_f = 0.20) afforded **2q** as a colorless oil (90 mg, 90%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.05-0.06 (m, 6H), 0.13 (m, 6H), 0.86 (s, 9H), 0.95 (s, 9H), 1.26 (s, 9H), 1.56 (s, 3H), 2.03-2.06 (m, 2H), 3.26 (s, 1H, *-OH*), 3.75 (d, *J*=3.4 Hz, 2H), 3.90-3.93 (m, 1H), 4.35-4.39 (m, 1H), 4.53 (s, 1H), 6.19 (t, *J*=6.9 Hz, 1H), 7.44-7.49 (m, 2H), 7.60-7.65 (m, 1H), 8.01-8.05 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) -5.2, -4.7, -4.6, 18.1, 18.7, 22.3, 25.8, 26.2, 27.7, 31.0, 39.3, 50.2, 63.9, 72.0, 72.7, 73.9, 85.4, 87.6, 95.5, 129.1, 130.6, 132.5, 134.8, 150.4, 168.4, 172.8 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{35}H_{56}N_2NaO_7Si_2$ $[M+Na]^+$ 695.3518, found 695.3512.

General procedure for the dehydration of 2a-2q to 3a-3q (Scheme 4)

Thionyl chloride (0.12 mmol, 8.7 µL) was added to a solution of the desired dihydrothymidine alcohol (0.1 mmol) in benzene (1.5 mL) and stirred for 1 min. Pyridine (2.4 mmol, 193 µL) was added and the solution was refluxed for 1-3 h depending on substrates. Then, EtOAc (20 mL) and water (7 mL) were added, the organic layer separated, washed with brine (10 mL) and dried over $NaSO_4$. The solvent was evaporated *in vacuo* to give the crude product, which was purified by flash column chromatography.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-phenylpyrimidine-2,4(1H,3H)-dione (**3a**).

Reflux for 1h. Column chromatography (EtOAc:Hexane 1:7, R_f = 0.30) gave **3a** as a colorless oil (62 mg, 95%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.05 (m, 6H), -0.01-0.01 (m, 6H), 0.75 (s, 9H), 0.84 (s, 9H), 1.65 (s, 3H), 1.73-1.82 (m, 1H), 2.86-2.94 (m, 1H), 3.58-3.65 (m, 3H), 4.25-4.31 (m, 1H), 5.40-5.44 (m, 1H), 7.17-7.20 (m, 1H), 7.42-7.45 (m, 1H), 7.49-7.55 (m, 5h), 7.64-7.69 (m, 1H), 7.99-8.03 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) -5.1, -5.0, -4.7, -4.6, 12.4, 17.8, 18.6, 25.8, 26.1, 38.1, 64.2, 72.5, 88.1, 88.5, 109.7, 127.9, 128.6, 129.2, 129.4, 129.7, 130.0, 130.8, 131.9, 132.6, 135.1, 148.8, 151.7, 162.9, 169.5 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{35}H_{50}N_2NaO_6Si_2$ $[M+Na]^+$ 673.3100, found 673.3081.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(2,6-dimethylphenyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3c**).

2c comprised of a mixture of *cis*-diastereomers (dr = 4:1), which both dehydrated to **3c**. Reflux for 3h. Column chromatography (EtOAc:Hexane 1:7, R_f = 0.40) gave **3c** as a colorless oil (62 mg, 91%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.05-0.00 (m, 12H), 0.76 (s, 9H), 0.83 (s, 9H), 1.56 (s, 3H), 1.76-1.82 (m, 1H), 2.16 (s, 3H), 2.32 (s, 3H), 2.84-2.89 (m, 1H), 3.62 (m, 3H), 4.29-4.33 (m, 1H), 5.31-5.34 (m, 1H), 7.15-7.21 (m, 2H), 7.28-7.31 (m, 1H), 7.51-7.54 (m, 2H), 7.65-7.68 (m, 1H), 7.96-7.98 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) -5.1, -5.0, -4.7, -4.6, 11.1, 17.8, 18.5, 19.6, 19.8, 25.8, 26.1, 38.8, 64.2, 72.4, 88.1, 108.8, 128.2, 128.7, 129.3, 130.0, 130.7, 131.6, 131.8, 134.9, 135.1, 136.1, 148.8, 151.1, 163.0, 169.4 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{37}H_{54}N_2NaO_6Si_2$ $[M+Na]^+$ 701.3413, found 701.3407.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-(p-tolyl)pyrimidine-2,4(1H,3H)-dione (**3d**).

Reflux for 1h. Column chromatography (EtOAc:Hexane 1:7, R_f = 0.30) gave **3d** as a white solid (63 mg, 94%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.05 (s, 6H), -0.01-0.01 (m, 6H), 0.75 (s, 9H), 0.84 (s, 9H), 1.66 (s, 3H), 1.72-1.81 (m, 1H), 2.44 (s, 3H), 2.85-2.94 (m, 1H), 3.58-3.65 (m, 3H), 4.25-4.31 (m, 1H), 5.42-5.46 (m, 1H), 7.06 (d, *J*=7.8 Hz, 1H), 7.30-7.37 (m, 3H), 7.49 (m, 2H), 7.63-7.68 (m, 1H), 7.99-8.02 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) -5.1, -5.0, -4.74, -4.65, 12.4, 17.8, 18.5, 21.5, 25.7, 26.1, 38.0, 64.2, 72.5, 88.1, 88.5, 109.6, 127.8, 128.4, 129.2, 129.6, 130.0, 130.3, 130.8, 131.9, 135.0, 140.1, 148.8, 151.9, 162.9, 169.5 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{36}H_{52}N_2NaO_6Si_2$ $[M+Na]^+$ 687.3256, found 687.3255. **Mp** 136-139 ℃

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(3-methoxyphenyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3f**).

Reflux for 3h. Column chromatography (EtOAc:Hexane 1:5, R_f = 0.40) gave **3f** as a colorless oil (61 mg, 90%). With **3f**, all the carbon peaks of the deoxyribose and methoxyphenyl moieties in ^{13}C NMR spectrum appear as duplicates. Also, -CH_3 of thymine and –OCH_3 appear as duplicates in ^{1}H NMR spectrum. The same result was achieved by repeating the reaction. Mass spectroscopic analysis (ESI-TOF) of **3f** did not indicate the presence of any byproduct. However, the ^{1}H NMR signals of -OCH_3 and -CH_3 coalesced at higher temperature (T_c > 52 ℃ in benzene-d_6, see NMR spectra of **3f**), indicating the presence of conformational isomers (e.g. rotamers or the deoxyribose having other sugar puckering conformation[31]). Also, all the ^{13}C NMR signals of the sugar moiety were found coalesced at 70 ℃ (benzene-d_6). **^{1}H NMR** (300 MHz, $CDCl_3$) -0.04-0.01 (m, 12H), 0.76 (s, 9H), 0.84 (s, 9H), 1.67-.168 (m, 3H), 1.75-1.83 (m, 1 H), 2.84-2.95 (m, 1H), 3.62-3.64 (m, 3H), 3.86-3.87 (m, 3H), 4.25-4.32 (m, 1H), 5.41-5.47 (m, 1H), 6.70-6.77 (m, 1H), 6.98-7.04 (m, 2H), 7.40-7.54 (m, 3H), 7.63-7.69 (m, 1H), 7.99-8.02 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) -5.1, -5.0, -4.7, -4.6, 12.3, 17.3, 18.6, 25.7, 26.1, 38.1, 38.2, 55.5, 55.6, 64.2, 64.3, 72.5, 72.6, 88.1, 88.2, 88.5, 88.6, 109.6, 113.6, 113.8, 115.1, 116.1, 120.1, 120.7, 129.2, 130.6, 130.8, 131.0, 131.9, 133.7, 135.1, 148.8, 151.4, 160.2, 160.4, 162.9, 169.5 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{36}H_{52}N_2NaO_7Si_2$ $[M+Na]^+$ 703.3205, found 703.3210.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(3-fluorophenyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3g**).

Reflux for 3h. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.40) gave **3g** as a white solid (63 mg, 94%). As with *meta*-OMe substituted **3f**, the ^{13}C NMR signals of the 3-fluorophenyl moiety appear as duplicates, thus indicating the presence of conformers. ^{1}H NMR signals are in accordance with the product and mass spectroscopic analysis (ESI-TOF) did not indicate the presence of byproducts. **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.04 (s, 6H), -0.01-0.01 (m, 6H), 0.76 (s,9H), 0.85 (s, 9H), 1.67 (s, 3H), 1.74-1.84 (m, 1H), 2.88-2.96 (m, 1H), 3.62 (m, 3H), 4.26-4.32 (m, 1H), 5.35-5.41 (m, 1H), 6.93-7.01 (m, 1H), 7.19-7.26 (m, 2H), 7.50-7.55 (m, 3H) 7.64-7.70 (m, 1H), 7.99-8.02 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -5.0, -4.7, -4.6, 12.3, 17.8, 18.5, 25.7, 26.1, 38.0, 64.1, 72.5, 88.2, 88.6, 110.0, 115.3 (d, *J* (C,F) = 22.5 Hz), 116.1 (d, *J* (C,F) = 22.5 Hz), 117.2 (d, *J* (C,F) = 20.6 Hz), 123.8, 124.5, 129.3, 130.8, 131.3 (d, *J* (C,F) = 7.6 Hz), 131.7 (d, *J* (C,F) = 7.8 Hz), 131.8, 134.4 (br s), 135.1, 148.6, 150.1, 162.7, 163.2 (d, *J* (C,F) = 251.9 Hz), 169.2 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{35}H_{49}FN_2NaO_6Si_2$ $[M+Na]^+$ 691.3005, found 691.2997. **Mp** 75-76 ℃.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(4-fluorophenyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3i**).

Reflux for 3h. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.40) gave **3i** as a white solid (62 mg, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.04-0.01 (m, 12H), 0.76 (s, 9H), 0.85 (s, 9H), 1.66 (s, 3H), 1.73-1.81 (m, 1H), 2.87-2.96 (m, 1H), 3.62 (s, 3H), 4.27-4.32 (m, 1H), 5.36-5.41 (m, 1H), 7.20-7.29 (m, 2H), 7.43-7.55 (m, 4H), 7.64-7.69 (m, 1H), 7.98-8.01 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -5.0, -4.7, -4.6, 12.4, 17.8, 18.5, 25.7, 26.1, 38.0, 64.1, 72.5, 88.1, 88.5, 110.2, 116.6, 116.9 (app t, *J* (C,F) = 20.8 Hz), 128.6 (br s), 129.2, 130.1 (d, *J* (C,F) = 8.0 Hz), 130.8, 131.8, 135.1, 148.7, 150.6, 162.7, 163.5 (d, *J* (C,F) = 250.8 Hz), 169.3 ppm; **^{19}F NMR** (160 MHz, $CDCl_3$) -110.21 (m) ppm; **HRMS** (ESI$^+$) *m/z* calcd for $C_{35}H_{49}FN_2NaO_6Si_2$ $[M+Na]^+$ 691.3005, found 691,3006. **Mp** 57-58 ℃.

6-(benzofuran-2-yl)-3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3j**).

Reflux for 2h. Column chromatography (EtOAc:Hexane 1:6, R_f = 0.35) gave **3j** as a colorless oil (64 mg, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.06-(-0.05) (m, 6H), -0.02-0.00 (m, 6H), 0.70 (s, 9H), 0.84 (s, 9H), 1.93 (s, 3H), 1.93-2.02 (m, 1H), 2.94-2.99 (m, 1H), 3.58-3.67 (m, 3H), 4.28-4.31 (m, 1H), 5.40-5.43 (m, 1H), 7.07 (s, 1H), 7.34-7.45 (m, 2H), 7.51-7.59 (m, 3H), 7.65-7.71 (m, 2H), 7.99-8.01 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -5.0, -4.8, -4.6, 12.5, 17.8, 18.6, 25.6, 26.1, 38.5, 64.1, 72.5, 88.4, 89.8, 111.3, 112.0, 113.9, 122.2, 124.1, 126.5, 127.3, 129.3, 130.8, 131.7, 135.2, 141.4, 145.0, 148.5, 155.1, 162.5, 168.9 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{37}H_{50}N_2NaO_7Si_2$ $[M+Na]^+$ 713.3049, found 713.3039.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(furan-3-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3k**).

Reflux for 2h. Column chromatography (EtOAc:Hexane 1:5, R_f = 0.38) gave **3k** as a colorless oil (54 mg, 88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.02-0.02 (m, 12H), 0.80 (s, 9H), 0.85 (s, 9H), 1.82 (s, 3H), 1.85-1.91 (m, 1H), 2.89-2.94 (m, 1H), 3.64-3.68 (m, 3H), 4.31-4.34 (m, 1H), 5.70-5.73 (m, 1H), 6.53 (s, 1H), 7.49-7.52 (m, 2H), 7.61 (s, 2H), 7.64-7.67 (m, 1H), 7.97-7.99 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -5.0, -4.7, -4.6, 12.7, 17.9, 18.6, 25.8, 26.1, 38.2, 64.2, 72.5, 88.2, 88.4, 110.7, 111.3, 117.1, 129.2, 130.8, 131.8, 135.1, 142.3, 144.1, 144.6, 148.8, 162.6, 169.2 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{33}H_{48}N_2NaO_7Si_2$ $[M+Na]^+$ 663.2892, found 663.2882.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-(thiophen-2-yl)pyrimidine-2,4(1H,3H)-dione (**3m**).

Reflux for 2h. Column chromatography (EtOAc:Hexane 1:4, R_f = 0.50) gave **3m** as a colorless oil (54 mg, 88%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.03-0.01 (m, 12H), 0.78 (s, 9H), 0.84 (s, 9H), 1.77 (s, 3H), 1.82-1.88 (m, 1H), 2.89-2.94 (m, 1H), 3.64 (m, 3H), 4.30-4.32 (m, 1H), 5.55-5.58 (m, 1H), 7.16-7.20 (m, 2H), 7.50-7.53 (m, 2H), 7.58 (m, 1H), 7.64-7.67 (m, 1H), 7.99-8.01 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -5.0, -4.7, -4.6, 12.7, 17.9, 18.6, 25.8, 26.1, 38.2, 64.2, 72.6, 88.3, 88.7, 112.9, 128.0, 129.1, 129.3, 129.8, 130.8, 131.8, 131.9, 135.1, 144.9, 148.6, 162.3, 169.2 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{33}H_{48}N_2NaO_6SSi_2$ $[M+Na]^+$ 679.2664, found 679.2667.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-(prop-1-yn-1-yl)pyrimidine-2,4(1H,3H)-dione (**3n**).

Reflux for 2h. Column chromatography (EtOAc:Hexane 1:5, R_f = 0.30) gave **3n** as a colorless oil (57 mg, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.00-0.04 (m, 12H), 0.85 (s, 9H), 0.87 (s, 9H), 2.08 (m, 4H), 2.22 (s, 3H), 2.89-2.98 (m, 1H), 3.67-3.69 (m, 2H), 3.81-3.86 (m, 1H), 4.36-4.42 (m, 1H), 6.58-6.63 (m, 1H), 7.45-7.51 (m, 2H), 7.60-7.66 (m, 1H), 7.91-7.93 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -5.0, -4.6, -4.5, 5.2, 12.9, 18.0, 18.6, 25.8, 26.2, 38.2, 64.2, 70.9, 72.7, 88.4, 89.2, 105.3, 115.1, 129.2, 130.7, 131.8, 134.9, 135.0, 148.3, 162.3, 169.0 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{32}H_{48}N_2NaO_6Si_2$ $[M+Na]^+$ 635.2943, found 635.2947.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methyl-6-(phenylethynyl)pyrimidine-2,4(1H,3H)-dione (**3o**).

Reflux for 2h. Column chromatography (EtOAc:Hexane 1:6, R_f = 0.40) gave **3o** as a colorless oil (65 mg, 96%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 0.00-0.03 (m, 12H), 0.86 (m, 18H), 2.08-2.20 (m, 4H), 2.98-3.07 (m, 1H) 3.68-3.70 (m, 2H), 3.84-3.90 (m, 1H), 4.39-4.44 (m, 1H), 6.69 (dd, *J*=7.7, 6.2 Hz, 1H), 7.40-7.52 (m, 5H), 7.57-7.67 (m, 3H), 7.93-7.96 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.11, -5.05, -4.7, -4.5, 13.1, 18.0, 18.6, 25.9, 26.2, 38.2, 64.2, 72.9, 79.4, 88.4, 89.4, 106.7, 115.7, 120.6, 128.9, 129.2, 130.7, 131.7, 132.1, 134.6, 135.1, 148.3, 162.1, 168.9 ppm;**HRMS** (ESI$^+$) *m/z* calcd. for $C_{37}H_{50}N_2NaO_6Si_2$ $[M+Na]^+$ 697.3100, found 697.3095.

3-benzoyl-6-((3,5-bis(trifluoromethyl)phenyl)ethynyl)-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3p**).

Reflux for 3h. Column chromatography (EtOAc:Hexane 1:6, R_f = 0.38) gave **3p** as a colorless oil (76 mg, 94%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.01-0.03 (m, 12H), 0.83 (s, 9H), 0.84 (s, 9H), 2.09-2.17 (m, 1H), 2.22 (s, 3H), 3.00-3.08 (m, 1H), 3.67-3.69 (m, 2H), 3.85-3.91 (m, 1H), 4.39-4.44 (m, 1H), 6.56 (dd, *J*=7.6, 6.0 Hz, 1H), 7.48-7.53 (m, 2H), 7.64-7.69 (m, 1H), 7.92-7.99 (m, 5H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.13, -5.08, -4.7, -4.6, 13.3, 17.9, 18.6, 25.8, 26.1, 38.1, 64.1, 72.8, 81.8, 88.6, 89.8, 101.9, 117.4, 120.9, 123.0, 124.0, 124.6, 128.2, 129.3, 130.7, 131.6, 131.8, 132.6, 133.1, 133.4, 135.2, 148.1, 161.8, 168.6 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{39}H_{48}F_6N_2NaO_6Si_2$ $[M+Na]^+$ 833.2847, found 833.2841.

3-benzoyl-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-6-(3,3-dimethylbut-1-yn-1-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**3q**).

Reflux for 1h. Column chromatography (EtOAc:Hexane 1:7, R_f = 0.37) gave **3q** as a colorless oil (61 mg, 93%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ -0.01-0.01 (m, 6H), 0.04-0.04 (m, 6H), 0.84 (s, 9H), 0.85 (s, 9H), 1.38 (s, 9H), 2.00-2.06 (m, 4H), 2.95-3.04 (m, 1H), 3.65-3.68 (m, 2H), 3.82-3.87 (m, 1H), 4.37-4.42 (m, 1H), 6.54-6.58 (m, 1H), 7.45-7.50 (m, 2H), 7.61-7.66 (m, 1H), 7.89-7.93 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.1, -5.0, -4.63, -4.55, 12.9, 18.0, 18.6, 25.9, 26.1, 29.1, 30.4, 37.8, 64.2, 70.4, 73.0, 88.5, 89.7, 114.6, 117.5, 129.2, 130.7, 131.8, 135.0, 135.3, 148.3, 162.3, 169.0 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{35}H_{54}N_2NaO_6Si_2$ $[M+Na]^+$ 677.3413, found 677.3405.

N3-debenzoylation of 3o to 4 (Scheme 5)

To solution of **3p** (50 mg, 0.062 mmol) in $CHCl_3$ (1 mL), 20 µL *n*-butylamine(0.19 mmol, 3 equiv) was added and stirred at room temperature for 2 h. Then the solvent was evaporated *in vacuo*, and the resulting crude mixture flash column chromatographed through silica gel (EtOAc:hexane 1:5, R_f = 0.20) to afford **4** as a white solid (41 mg, 95%).

6-((3,5-bis(trifluoromethyl)phenyl)ethynyl)-1-((2R,4S,5R)-4-((tert-butyldimethylsilyl)oxy)-5-(((tert-butyldimethylsilyl)oxy)methyl)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**4**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06-0.07 (m, 12H), 0.85 (s, 9H), 0.89 (s, 9H), 2.06-2.14 (m, 1H), 2.19 (s, 3H), 3.03-3.12 (m, 1H), 3.74-3.87 (m, 2H), 3.89-3.92 (m, 1H), 4.49-4.54 (m, 1H), 6.48-6.53 (m, 1H), 7.96 (s, 3H), 8.50 (s, 1H, *-NH*) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ -5.13, -5.09, -4.7, -4.6, 13.2, 18.0, 18.6, 25.8, 26.1, 37.8, 64.0, 73.0, 82.0, 88.3, 89.5, 101.4, 117.5 122.7 (q, ^1J (C,F) = 273.6 Hz), 123.1, 123.9, 131.8, 132.8 (q, ^2J (C,F) = 34.2 Hz), 133.6, 148.8, 162.5 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{32}H_{44}F_6N_2NaO_5Si_2$ $[M+Na]^+$ 729.2585, found 729.2599. **Mp** 63-67 ℃.

Synthesis of 7 (Scheme 6)

O,O-Acetyl protection of Thymidine.

The modified procedure described previously was used.[32] To a solution of thymidine (1.0 g, 4.1 mmol) in DMF (10 mL) under argon were added pyridine (1.3 mL, 16 mmol), 4-dimethylaminopyridine (DMAP, 50 mg, 0.41) and acetic anhydride (1.1 mL, 12 mmol). The resulting solution was stirred at rt. for 14 h. Then, sat.aq. $NaHCO_3$ (15 mL) and EtOAc (60 mL) were added, the organic layer was separated, washed with water (5 × 15 mL), brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford *O*,*O*-Ac-thymidine as light yellow oil (1.18 g, 88%), which was used for the next step without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.93 (d, *J* = 1.2 Hz, 3H), 2.10-2.20 (m, 1H), 2.10 (s, 3H), 2.12 (s, 3H), 2.43-2.50 (m, 1H), 4.22-4.25 (m, 1H), 4.33-4.36 (m, 2H), 5.19-5.23 (m, 1H), 6.32 (dd, *J* = 8.5, 5.6 Hz, 1H), 7.26 (d, *J* = 1.2 Hz, 1H), 9.28 (br s, 1H, *-NH*) ppm.

N-benzoylation of O,O-Ac-thymidine.

The procedure described previously was used.[16] To a solution of *O*,*O*-Ac-thymidine (1 g, 3.06 mmol) in MeCN (15 mL) under argon were added triethylamine (0.85 mL, 6.12 mmol), pyridine (0.25 mL, 3.06 mmol) and benzoyl chloride (0.4 mL, 3.4 mmol). The resulting slurry was heated at 80 °C for 1 h with vigorous stirring. Water (1 mL) was added and stirring continued while the mixture was cooled down to room temperature. 2 M NaOH (15 mL) and EtOAc (70 mL) were added and stirred until all the solids were dissolved. The organic phase was separated, washed with 2 M HCl (2 × 15 mL), 1 M NaOH (2 ×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*-Ac-thymidine as light brown oil (1.24 g, 94 %), which was used in the next step without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 1.97 (d, *J* = 1.2 Hz, 3H), 2.08 (s, 3H), 2.14 (s, 3H), 2.17-2.26 (m, 1H), 2.42-2.52 (m, 1H), 4.24-4.27 (m, 1H), 4.33-4.41 (m, 2H), 5.20-5.23 (m, 1H), 6.30 (dd, *J* = 8.4, 5.7 Hz, 1H), 7.38 (d, *J* = 1.2 Hz, 1H), 7.46-7.51 (m, 2H), 7.62-7.67 (m, 1H), 7.90-7.92 (m, 2H) ppm.

*Synthesis of thymidine trans-bromohydrin **5***.

The modified procedure described previously was used.[16] To a solution of *N*-Bz-*O*,*O*-Ac-thymidine (1.0 g, 2.32 mmol) in THF (12mL) was added water (1.2 mL) followed by the addition N-bromosuccinimide (1.65 g, 9.2 mmol). The resulting solution was stirred vigorously at room temperature for 50 min, whereupon water (10mL) and EtOAc (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), brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated *in vacuo* to give a crude product, which was purified by column chromatography (EtOAc:hexane 1:1, R_f = 0.45 for major and 0.40 for minor diastereomer) to afford a mixture of diastereomers (dr = 2:1, ^{1}H NMR, 0.80 g, 65%) as colorless oil, wherein (5R,6R) was the major diasteromer.[33]

Major diastereomer (5R,6R): **^{1}H NMR** (300 MHz, $CDCl_3$) 2.06 (s, 3H), 2.09 (s, 3H), 2.15 (s, 3H), 2.28-2.61 (m, 2H), 4.07-4-49 (m, 3H), 5.15-5.22 (m, 2H), 5.21 (br s, 1H, -OH), 6.44 (dd, *J* = 8.7, 6.2 Hz, 1H), 7.45-7.50 (m, 2H), 7.61-7.66 (m, 1H), 7.99-8.02 (m, 2H) ppm. 1.38 (s, 9H), 2.00-2.06 (m, 4H), 2.95-3.04 (m, 1H), 3.65-3.68 (m, 2H), 3.82-3.87 (m, 1H), 4.37-4.42 (m, 1H), 6.54-6.58 (m, 1H), 7.45-7.50 (m, 2H), 7.61-7.66 (m, 1H), 7.89-7.93 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 20.96, 21.02, 23.1, 35.6, 53.7, 64.0, 73.7, 80.2, 81.6, 84.6, 129.2, 130.5, 132.0, 135.1, 149.9, 165.7, 167.8, 171.2 ppm; **HRMS** (ESI^+) *m/z* calcd. for $C_{21}H_{23}BrN_2NaO_9$ $[M+Na]^+$ 549.0479, found 549.0459.

Minor diastereomer (5S,6S): **^{1}H NMR** (300 MHz, $CDCl_3$) 1.99 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.28-2.61 (m, 2H), 4.07-4-49 (m, 3H), 4.77 (br s, 1H, -OH), 5.15-5.22 (m, 2H), 6.07 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.45-7.50 (m, 2H), 7.61-7.66 (m, 1H), 7.99-8.02 (m, 2H) ppm. **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 20.96, 21.02, 22.8, 35.0, 53.6, 68.8, 74.5, 80.3, 81.7, 85.7, 129.2, 130.5, 132.2, 135.1, 149.4, 166.3, 168.6, 170.7 ppm; **HRMS** (ESI^+) *m/z* calcd. for $C_{21}H_{23}BrN_2NaO_9$ $[M+Na]^+$ 549.0479, found 549.0459.

*Synthesis of **6a** and **6b** from **5**.*

To a solution of **5** (0.25 g, 0.47 mmol, mixture of *trans*-diastereomers, dr = 2:1) in dry acetone (5 mL) under argon was added triethylamine (80 µL, 0.56 mmol) at room temperature. The mixture was gently shaken and left standing for 60 minutes (with no shaking!) to allow triethylamine hydrobromide precipitation as transparent needles. The supernatant was then transferred into another flask under argon using a syringe (Ø 0.6 mm × 25 mm needle). The remaining precipitate was washed with dry acetone (2×1.0 mL) and the combined solvents were evaporated *in vacuo* to afford the mixture of epoxides as a white foamy solid, which was then dissolved in MeCN (5 mL). To this solution was added potassium propynyltrifluoroborate (89 mg, 0.61 mmol), followed by the addition of $BF_3{\cdot}OEt_2$ (0.47 mmol, 58 µL) under inert atmosphere. The mixture was stirred for 30 min and then quenched with sat.aqueous $NaHCO_3$ (5 mL) with vigorous stirring for 5 min. EtOAc (40 mL) and sat. aqueous $NaHCO_3$ (10 mL) were added, the organic layer separated, washed once with brine (10 mL), dried over $NaSO_4$, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (EtOAc-Hex 1:1) to afford the products **6a** (135 mg, 59%, R_f = 0.20 and **6b** (64 mg, 28%, R_f = 0.30) as colorless oils.

((2R,3S,5R)-3-acetoxy-5-((5S,6R)-3-benzoyl-5-hydroxy-5-methyl-2,4-dioxo-6-(prop-1-yn-1-yl)tetrahydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (**6a**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.92 (d, *J*=2.1 Hz, 3H), 2.07 (s, 3H), 2.13 (s, 3H), 2.26-2.30 (m, 2H), 3.49 (s, 1H, *-OH*), 4.17-4.40 (m, 4H), 5.20-5.23 (m, 1H), 6.17 (dd, *J*=8.1, 6.3 Hz, 1H), 7.44-7.49 (m, 2H), 7.61-7.66 (m, 1H), 8.02-8.05 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 3.8, 21.0, 22.8, 35.8, 51.1, 64.2, 72.1, 74.0, 74.5, 81.6, 83.4, 85.4, 129.2, 130.7, 132.1, 135.1, 150.5, 167.9, 170.5, 172.5 ppm; **HRMS** (ESI^+) *m/z* calcd. for $C_{24}H_{26}N_2NaO_9$ $[M+Na]^+$ 509.1531, found 509.1545.

((2R,3S,5R)-3-acetoxy-5-((5R,6S)-3-benzoyl-5-hydroxy-5-methyl-2,4-dioxo-6-(prop-1-yn-1-yl)tetrahydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (**6b**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H), 1.94 (d, *J*=2.5 Hz, 3H), 2.07 (s, 3H), 2.16 (s, 3H), 2.19-2.29 (m, 1H), 2.51-2.61 (m, 1H), 3.47 (s, 1H, *-OH*), 4.14-4.17 (m, 1H), 4.26-4.37 (m, 2H), 4.49-4.51 (m, 1H), 5.20-5.23 (m, 1H) 6.25 (dd, *J*=9.1, 5.5 Hz, 1H), 7.45-7.50 (m, 2H), 7.61-7.66 (m, 1H), 7.97-8.00 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 3.7, 20.9, 21.0, 22.9, 34.5, 48.9, 64.1, 71.9, 74.2, 74.6, 81.2, 84.1, 84.3, 129.2, 130.5, 132.3, 135.0, 149.9, 168.0, 170.5, 172.7 ppm;**HRMS** (ESI^+) *m/z* calcd. for $C_{24}H_{26}N_2NaO_9$ $[M+Na]^+$ 509.1531, found 509.1536.

*Dehydration of **6a** and **6b** to **7**.*

Thionyl chloride (0.2 mmol, 14.5 µL) was added to a solution of a mixture of **6a** (40 mg, 0.082 mmol) and **6b** (40 mg, 0.082 mmol) in benzene (1.5 mL) and stirred for 1 min. Pyridine (3.3 mmol, 265 µL) was added and the solution was refluxed for 2h, whereupon EtOAc (30 mL) and water (7 mL) were added, the organic layer separated, washed with brine (10 mL) and dried over Na_2SO4. The solvent was evaporated *in vacuo* to give the crude product, which was purified by flash column chromatography (EtOAc-Hex, 1:1, R_f = 0.4) to give **7** as a white powder (73 mg, 95%).

((2R,3S,5R)-3-acetoxy-5-(3-benzoyl-5-methyl-2,4-dioxo-6-(prop-1-yn-1-yl)-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (**7**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.05 (s, 3H), 2.09 (s, 3H), 2.26-2.34 (m, 4H), 3.12-3.22 (m, 1H), 4.10-4.18 (m, 2H), 4.38-4.46 (m, 1H), 5.34-5.41 (m, 1H), 6.63 (dd, *J*=8.7, 4.8 Hz, 1H), 7.46-7.51 (m, 2H), 7.62-7.67 (m, 1H), 7.90-7.93 (m, 1H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 5.3, 12.9, 20.9, 36.2, 64.1, 70.8, 74.3, 82.7, 88.6, 105.6, 115.9, 129.3, 130.7, 131.6, 134.1, 135.2, 148.5, 162.0, 168.6, 170.2, 170.8 ppm; **HRMS** (ESI^+) *m/z* calcd. for $C_{24}H_{24}N_2NaO_8$ $[M+Na]^+$ 491.1425, found 491.1425. **Mp** 165-168 ℃.

Synthesis of 10 (Scheme 6)

Synthesis of N-PMB-O,O-Ac-Thymidine.

To a solution of *O*,*O*-Ac-thymidine (1 g, 3.06 mmol) in DMF (10 mL) under argon was added K_2CO_3 (0.62 g, 4.5 mmol) and 4-methoxybenzyl chloride (PMB-Cl, 0.43 mL, 3.2 mmol). The resulting mixture was stirred at room temperature for 14 h, whereupon EtOH (1.0 mL) was added and stirred for 10 min. Then, water (30 mL) and Et_2O (80 mL) were added, the organic phase was separated, washed with water (2×20 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 1:1, R_f = 0.40) to afford *N*-PMB-*O*,*O*-Ac-thymidine as amorphous solid (1.25 g, 91%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.09 (s, 3H), 2.10 (s, 3H), 2.06-2.17 (m, 1H), 2.42-2.49 (m, 1H), 3.76 (s, 3H), 4.18-4.27 (m, 1H), 4.32-4.34 (m, 1H), 5.05 (s, 2H), 5.18-5.21 (m, 1H), 6.34 (dd, *J*=8.5, 5.6 Hz, 1H), 6.76-6.86 (m, 2H), 7.24 (s, 1H), 7.39-7.49 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 13.6, 21.0, 37.7, 44.1, 55.3, 63.9, 74.2, 82.1, 85.6, 110.9, 113.8, 129.2, 130.9, 132.6, 151.0, 159.2, 163.2, 170.2, 170.4 ppm.

*Synthesis of thymidine trans-bromohydrin **8**.*

The modified procedure used with *N*-Bz-Thymidine was applied to avoid bromination of the PMB group. To a solution of *N*-PMB-*O*,*O*-Ac-thymidine (0.5 g, 1.12 mmol) in THF (15mL) was added water (1.5 mL) followed by the addition N-bromosuccinimide (0.20 g, 1.12 mmol, 1 equiv). The resulting solution was stirred vigorously at room temperature and monitored by TLC (EtOAc:hex 1:1). Every 30 min 0.1 equiv of NBS (0.05g 0.11 mmol) was added until the starting material was consumed (TLC). After 1.5 h the reaction was completed (1.3 equiv of NBS), whereupon water (10mL) and Et_2O (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 washed with water (2 × 10 mL), brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated *in vacuo* to give the crude product as a mixture of *trans* diastereomers (dr = 3:2, ^{1}H NMR). The purification by column chromatography (EtOAc:$CHCl_3$ 1:4) afforded the major diastereomer **8** as a white solid (0.265 g, 44%, R_f = 0.40) and the minor diastereomer as a colorless oil (0.170 g, 28 % R_f = 0.20). Only ^{1}H and ^{13}C NMR data are reported for the minor diastereomer.

*Major diastereomer **8** (5R,6R):* **^{1}H NMR** (300 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.17-2.42 (m, 2H), 3.61 (d, *J*=2.4, 1H), 3.76 (s, 3H), 4.10-4.13 (m, 1H), 4.26 (dd, *J*=12.1, 3.0 Hz, 1H), 4.40 (dd, *J*=12.1, 4.9 Hz, 1H), 4.95 (q, J=14.3 Hz, 2H), 5.09 (d, *J*=2.4 Hz, 1H), 5.14 (dt, *J*= 6.4, 2.8 Hz, 1H), 6.42-6.59 (m, 1H), 6.69-6.90 (m, 2H), 7.17-7.38 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 21.0, 23.8, 34.8, 44.5, 53.7, 55.3, 64.0, 73.8, 79.6, 81.4, 85.4, 113.9, 129.0, 129.7, 151.3, 159.0, 166.7, 170.6, 171.0 ppm. **HRMS** (ESI$^+$) *m/z* calcd. for $C_{22}H_{27}BrN_2NaO_9$ $[M+Na]^+$ 565.0792, found 565.0802. **Mp** 132-134 ℃.

Minor diastereomer (5S,6S): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.08 (s, 3H), 2.09 (s, 3H), 2.33-2.55 (m, 2H), 3.76 (s, 3H), 3.83 (d, *J*=5.5, 1H), 4.10-4.30 (m, 2H), 4.30-4.48 (m, 1H), 4.74-5.01 (m, 2H), 5.06-5.27 (m, 2H), 6.01 (dd, *J*=8.1, 6.0 Hz, 1H), 6.65-6.91 (m, 2H), 7.13-7.39 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 21.1, 23.6, 36.1, 44.4, 53.3, 55.4, 64.1, 74.6, 80.4, 81.9, 87.3, 113.9, 128.9, 129.7, 150.7, 159.0, 167.0, 170.8, 171.4 ppm.

*Synthesis of **9** from **8**.*

To a solution of **8** (200 mg, 0.37 mmol) in dry acetone (4 mL) under argon was added triethylamine (103 µL, 0.74 mmol) at room temperature. The mixture was gently shaken and left standing for 3 h to allow triethylamine hydrobromide precipitation as transparent needles. The supernatant was then transferred into another flask containing propynyltrifluoroborate (76 mg, 0.52 mmol) using a syringe (Ø 0.6 mm × 25 mm needle). The remaining precipitate (Et_3NBr) was washed once with cold dry MeCN (1.0 mL). Then, $BF_3{\cdot}OEt_2$ (0.37 mmol, 45 µL) was added and the mixture was stirred for 30 min, whereupon the reaction was quenched with sat. aq. $NaHCO_3$ (5 mL) with vigorous stirring for 5 min. EtOAc (30 mL) and water (10 mL) were added, the organic layer separated, washed once with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude material was purified by column chromatography (EtOAc:$CHCl_3$ 1:4, R_f = 0.3) to afford **9** (123 mg, 66%) as a foamy oil.

((2R,3S,5R)-3-acetoxy-5-((5S,6R)-5-hydroxy-3-(4-methoxybenzyl)-5-methyl-2,4-dioxo-6-(prop-1-yn-1-yl)tetrahydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (**9**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.64 (d, *J*=2.1 Hz, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.15-2.32 (m, 2H), 3.51 (s, 1H, -O*H*), 3.76 (s, 3H), 4.05-4.25 (m, 3H), 4.32 (dd, *J*=12.9, 4.8 Hz, 1H), 4.92 (s, 2H), 5.19 (dt, *J*=5.2, 2.6 Hz, 1H), 6.21 (dd, J=8.0, 6.4 Hz, 1H), 6.78-6.81 (m, 2H), 7.16-7.38 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 3.6, 20.9, 21.0, 23.1, 35.6, 44.4, 50.3, 55.3, 64.2, 71.4, 73.5, 74.6, 81.3, 82.4, 85.7, 113.8, 129.2, 130.0, 152.1, 159.0, 170.4, 170.5, 173.4 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{25}H_{30}N_2NaO_9$ $[M+Na]^+$ 525.1844, found 525.1847.

*Dehydration of **9** to **10**.*

Thionyl chloride (0.247 mmol, 18 µL) was added to a solution of **9** (100 mg, 0.206 mmol) in benzene (2.5 mL) and stirred for 1 min. Pyridine (4.1 mmol, 302 µL) was added and the solution was refluxed for 2h, whereupon EtOAc (30 mL) and water (7 mL) were added, the organic layer separated, washed with brine (7 mL) and dried over Na_2SO_4. The solvents were evaporated *in vacuo* to give the crude product, which was purified by flash column chromatography (EtOAc-hex, 1:1, R_f = 0.25) to give **10** as a colorless oil (94 mg, 94%).

((2R,3S,5R)-3-acetoxy-5-(3-(4-methoxybenzyl)-5-methyl-2,4-dioxo-6-(prop-1-yn-1-yl)-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (**10**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.19 (s, 3H), 2.26 (ddd, J=14.0, 8.7, 5.2 Hz, 1H), 3.12 (ddd, *J*=13.7, 8.6, 4.8 Hz, 1H), 3.76 (s, 3H), 4.05-4.21 (m, 1H), 4.28 (dd, *J*=11.5, 7.8 Hz, 1H), 4.50 (dd, *J*=11.5, 3.8 Hz, 1H), 5.01 (s, 2H), 5.39-5.59 (m, 1H), 6.62 (dd, *J*=8.7, 4.8 Hz, 1H), 6.74-6.87 (m, 2H), 7.35-7.51 (m, 2H) ppm; **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 5.1, 13.5, 21.0, 21.1, 36.4, 43.9, 55.3, 64.7, 70.9, 74.7, 82.6 88.8, 103.9, 113.8, 115.4, 129.1, 131.0, 132.2, 150.0, 159.2, 162.5, 170.4, 170.8 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{25}H_{28}N_2NaO_8$ $[M+Na]^+$ 507.1738, found 507.1723.

Removal of PMB from 10 (Scheme 6)

A procedure described previously was used.[30] To a solution of **10** (0.21 mmol, 100 mg) in MeCN (3 mL) was added CAN (0.84 mmol, 461 mg) in H_2O (0.3 mL). The mixture was heated at 70 ℃ for 1.5 h, whereupon water (10 mL) and EtOAc was added (10 mL). The organic layer was separated and the water layer was extracted with EtOAc (4×10). The combined organic layers were washed once with brine (10 mL), dried over Na_2SO_4,

and the solvents were evaporated *in vacuo* to give the crude product, which was purified by column chromatography (EtOAc-$CHCl_3$ 1:4 → 1:2, R_f = 0.05 for EtOAc-$CHCl_3$ 1:4) to afford **11** as a colorless oil (35 mg, 47%).

((2R,3S,5R)-3-acetoxy-5-(5-methyl-2,4-dioxo-6-(prop-1-yn-1-yl)-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-2-yl)methyl acetate (**11**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.08 (s, 6H), 2.22 (s, 3H), 2.25-2.31 (m, 1H), 3.15 (ddd, *J*=13.8, 8.5, 5.0 Hz, 1H), 4.05-4.45 (m, 2H), 4.49 (dd, *J*=11.4, 3.8 Hz, 1H), 5.39-5.46 (m, 1H), 6.59 (dd, *J*=8.5, 5.0 Hz, 1H), 8.44 (br s, 1H, N*H*); **^{13}C {^{1}H} NMR** (75 MHz, $CDCl_3$) δ 5.2, 12.9, 21.0, 21.1, 36.2, 64.5, 70.9, 74.5, 82.4, 88.2, 104.9, 116.0, 134.1, 149.2, 162.7, 170.3, 170.8 ppm; **HRMS** (ESI$^+$) *m/z* calcd. for $C_{17}H_{20}N_2NaO_7$ $[M+Na]^+$ 387.1163, found 387.1157.

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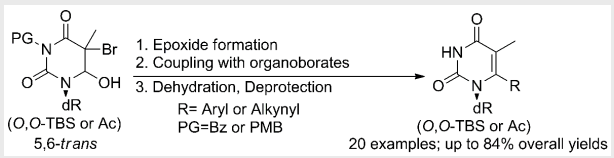

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Syntheses of C6 Aryl and Alkynyl Thymidines from Thymidine *trans*-5,6-Bromohydrins

Thymidine derivatization: A metal-free *cis*-diastereoselective coupling of thymidine 5,6-epoxides with various aryl- and alkynyltrifluoroborates followed by near-quantitative dehydration provide C6 aryl and alkynyl thymidines in high overall yields.