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Alternative Syntheses of (*S*)-cEt-BNA: A Key Constrained Nucleoside Component of Bioactive Antisense Gapmer Sequences

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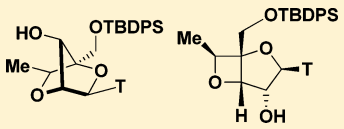
Supporting Information

ABSTRACT: Approaches to the synthesis of the constrained 5-methyluracil nucleoside (*S*)-cEt-BNA, a key "gapmer" unit in a number of biologically relevant antisense oligonucleotides, are described using 5-methyluridine as starting material. In the shorter synthesis, a nine-step linear sequence afforded a O-protected (*S*)-cEt-BNA consisting of a [2.2.1]-dioxabicycloheptane core in 7% overall yield. A competing reaction in an intramolecular cyclization of a tosylate led to a bicyclic oxetane.



INTRODUCTION

The study and application of antisense technology as an alternative to small molecule drug therapy has grown considerably in recent years.[1] An important structural element in the elaboration of a given antisense sequence is to include chemically modified nucleoside units at strategic sites to achieve the most effective "gapmer" design.[2] Incorporation of such modified unnatural nucleosides has led to overall better recognition and hybridization with target complementary DNA or RNA, increased stability toward degradation by RNase H, and potentially low toxicity to animals.[3]

Imanishi,[4] Wengel,[5] and their respective co-workers were the first to report the synthesis and improved hybridization properties of bicyclic 2′-*O*,4′-*C*-methylene nucleosides, also termed 2′,4′-bridged, constrained, or locked nucleosides (LNA). These consist of a [2.2.1]dioxabicycloheptane core, with an appended nucleobase at 1′, a hydroxyl group at 3′, and a hydroxymethyl group at 4′ (for internucleotide phosphate linking) (Figure 1a). Examples of related 2′-*O*,4′-*C*-methylene-bridged nucleosides have been reported more recently.[6−8]

Extensive studies have established the existence of two types of sugar pucker in nucleosides designated as "northern" (C3′-endo-C2′-exo) and "southern" (C2′-endo-C3′-exo) conformations (Figure 1b).[9] The rationale for the incorporation of such modified nucleosides in a given antisense oligonucleotide (ASO) sequence is to achieve effective hybridization with single-stranded RNA or double-stranded DNA, thus benefiting from a negative entropy change during duplex or triplex formation.[10] In an ideal situation, the melting temperature (T_m) would be favorably increased, reflecting on a higher stability compared to the native DNA segment.

Extensive studies by scientists at Isis Pharmaceuticals have shown that an ASO containing a central DNA region harboring 8−14 nucleotides and flanked by 2−5 2′-O-methoxyethyl (MOE) nucleoside residues occupying the 3′- and 5′-ends supports RNase H-mediated degradation of target mRNA (Figure 1).[11] As a result, this combination enjoys a privileged position as a second generation ASO in nearly 30 ongoing human clinical trials involving a number of disease indications.

In an effort to reduce possible hepatotoxicity in mice while maintaining potency, Seth, Swayze, and co-workers synthesized a 2′,4′-constrained MOE nucleoside (cMOE) (Figure 1c).[12] This branched analogue can be considered as a tethered 2′-MOE nucleoside in which one of the methylene groups is tethered to C4′, thus generating two possible epimers at the 6′-position. Although these BNAs (bridged nucleic acid) had a positive impact on reducing hepatotoxicity, they were surprisingly less potent than the parent LNA. This was attributed to an increase in steric bulk due to the CH_2OMe group. Consequently, the corresponding (*R*) and (*S*)-cEt analogues were synthesized, where the terminal *O*-methyl was removed. Interestingly, the (*S*)-cEt 2′,4′-bridged nucleoside (cEt-BNA) was found to be more potent (ED_{50} = 9 mg/kg; IC_{50} = 5.8 nM) compared to the (*R*)-epimer. (*S*)-cEt-modified ASOs currently represent the next generation oligonucleotide design platform, and several (*S*)-cEt-modified ASOs have already progressed into human clinical trials.[13−15] This finding introduced a new generation of stereochemically unique 2′,4′-bridged nucleosides requiring the development of various synthetic approaches. The synthesis and biophysical evaluation of this series of constrained nucleosides was recently reported by Isis Pharmaceuticals scientists.[16] Starting with the commercially available 1,2:5,6-di-*O*-isopropylidene-D-allofuranose prepared from D-glucose in 55% yield over three steps,[17] a series of sterocontrolled reactions eventually led to an appropriately C4′ branched intermediate which was subjected to intramolecular cyclization to the 2′,4′-oxabridge followed by introduction of the nucleobase, typically a uracil group, to yield an *O*-TBDPS-protected cEt-BNA.

While the reported synthesis[16] is amenable to scale up, it is also quite lengthy, being over 20 steps, and requires a substantial amount of time to manufacture. Due to the

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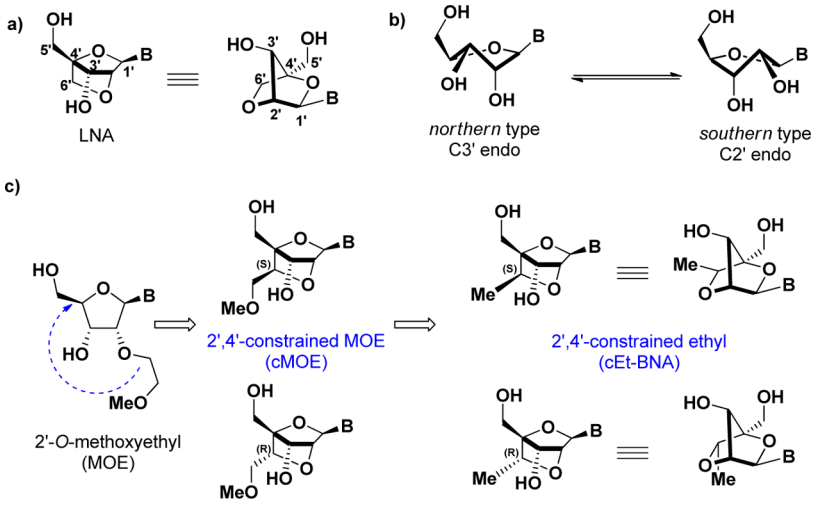


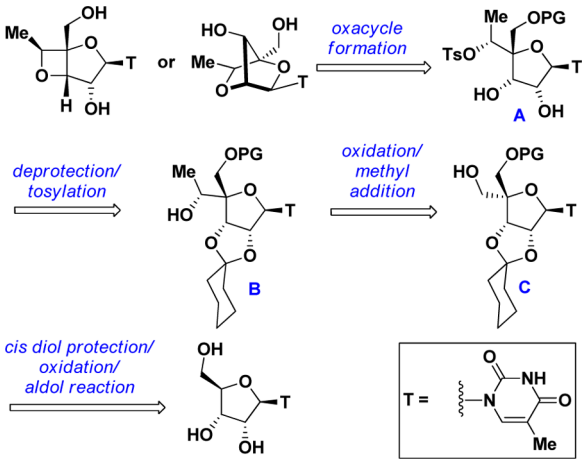
Figure 1. (a) Structure of LNA. (b) Northern and southern type conformations of the sugar ribose. (c) Rational analysis toward design of cEt-BNA nucleosides.

importance of the ongoing human clinical development of this new generation of stereochemically unique 2′,4′-bridged nucleosides, the development of alternate synthetic approaches for their commercial production is required. In our current approach, we sought to implement an inexpensive nucleoside, which has four of the required stereocenters already in place, as our starting material and take advantage of cuprate chemistry to decrease the number of steps and operation time by almost half.

RESULTS AND DISCUSSION

To the best of our knowledge, and except for the original Imanishi report,[4] previous approaches to the synthesis of LNA-related nucleosides utilized appropriate carbohydrate molecules as starting materials.[18−21] In particular, this strategy allowed the stereocontrolled introduction of a given nucleobase to give the β-D-4′-branched ribonucleoside, which was then elaborated further to incorporate the 2′,4′-oxamethylene bridge via an S_N2 displacement reaction. Inspired by the Imanishi synthesis of LNA starting with uridine, we envisaged that the 2′,4′-ether bridge in (*S*)-cEt-BNA can be formed via S_N2 displacement of an appropriate leaving group by the 2′ alcohol of nucleoside **A** (Scheme 1). This approach has been successfully applied in the synthesis of complex nucleosides bearing the protected 3′-OH.[18,21] In the case of the diol group in **A**, we would face a 4-exotet vs 5-exotet cyclization both favored by Baldwin's rules,[22] hoping that the formation of the four-membered ring oxetane to be less favored due to ring strain in the [2.1.1]-dioxabicycloheptane core structure. With this strategy in mind, the stereoselective addition of a methyl group to the corresponding aldehyde to obtain the (*R*)-alcohol **B** required particular attention. The desired configuration at C6′ would be achieved during an S_N2 displacement with inversion of configuration.

Scheme 1. Retrosynthetic Analysis of (*S*)-cEt-BNA



Starting from the low cost commercially available 5-methyluridine and protection of the *cis*-2′,3′-diol as a cyclohexylidene acetal, followed by oxidation of the primary alcohol using Dess−Martin periodinane[23] (DMP), led to an aldehyde which was subsequently subjected to a cross-aldol reaction with formaldehyde and one-pot reduction following the Moffatt protocol,[24] giving diol **1** in 62% yield over three steps (Scheme 2). Treatment of **1** with 1.3 equiv of TBSCl at 0 °C gave a 7:3 mixture of the α-C4′-hydroxymethyl ether as the major product. Addition of excess TBDPSCl to this mixture, followed by cleavage of the TBS ethers with TFA, afforded the C5′-hydroxymethyl TBDPS ether **2** in 60%.

Oxidation of **2** with DMP and further treatment of the resulting aldehyde with $AlMe_3$ produced diasteroselectively the C6′-(*S*)-alcohol **3** in 68% yield as a single isomer. To invert the configuration at C6′ of **3**, we used an oxidation−reduction sequence. Thus, oxidation of **3** with DMP and reduction of the crude ketone with $LiAlH_4$ at −78 °C afforded (*R*)-**4** as a single isomer.[16] Alternatively, treatment of the C6′ aldehyde with MeLi/CuI in MTBE (methyl *tert*-butyl ether) led directly to (*R*)-alcohol **4** in a ratio up to 8:1 in 51% yield over two steps. The use of MTBE as solvent proved to be beneficial compared to the same reaction with diethyl ether as solvent (4:1 ratio). With **4** in hand, the next step involved formation of the mesylate of the secondary alcohol and cleavage of the cyclohexylidene acetal under acidic conditions to give diol **5** in 52% yield over two steps. At this point, the first attempt to directly cyclize diol **5** to obtain the (*S*)-cEt-BNA led to the four-membered oxetane ring **6** via an 4-exotet cyclization mode[22] in 90% yield (Scheme 2). This result agrees with previous reports about the preferential formation of the oxetane product.[25,26] With the aim to complete the synthesis, it was

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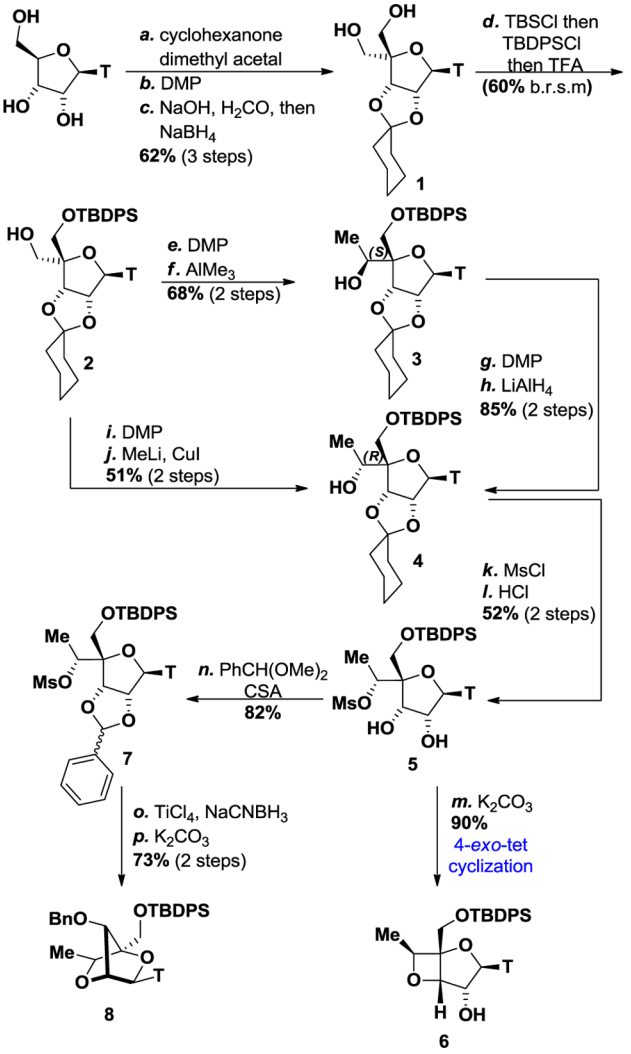
Scheme 2. Synthesis of Dioxabicyclo Nucleosides 6 and 8[a]

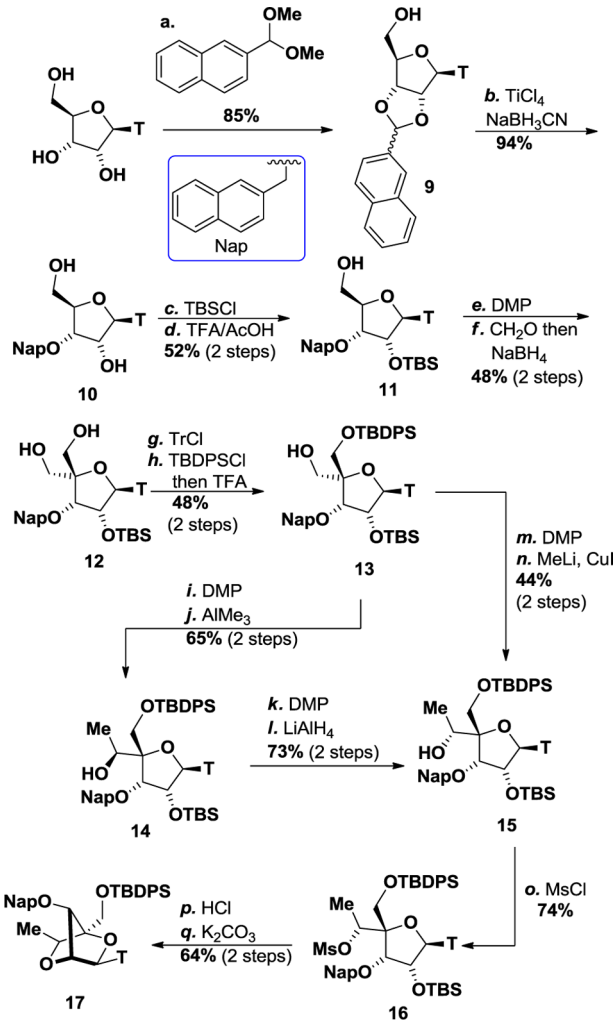


[a]Reagents and conditions: (a) cyclohexanone dimethyl acetal, CSA, 1,2-DCE; (b) DMP, $NaHCO_3$, CH_2Cl_2; (c) 37% formaldehyde, NaOH/THF, H_2O, then $NaBH_4$; (d) TBSCl, ImH, DMF, 0 °C, then TBDPSCl, then MeOH, TFA; (e) DMP, $NaHCO_3$, CH_2Cl_2; (f) $AlMe_3$, toluene; (g) DMP, $NaHCO_3$, CH_2Cl_2; (h) $LiAlH_4$, THF, −78 °C; (i) DMP, $NaHCO_3$, CH_2Cl_2; (j) MeLi, CuI, MTBE, 0 °C; (k) MsCl, pyridine; (l) HCl:THF:MeOH (3:4:2); (m) K_2CO_3, MeOH; (n) benzaldehyde dimethyl acetal, CSA, 1,2-DCE; (o) $TiCl_4$, $NaBH_3CN$, MeCN; (p) K_2CO_3, MeOH.

decided to use a detour by protecting the diol moiety in **5** as a benzylidene acetal. Selective reductive cleavage of the diastereomeric mixture of acetals in **7** was achieved by treatment with $TiCl_4/NaBH_3CN$[27] to furnish the 2′-OH free nucleoside, which readily cyclized under basic conditions to give **8**. However, different attempts to cleave the benzyl ether in **8** via hydrogenolysis were unsuccessful ($Pd(OH)_2$, Pd/C). When harsher conditions were employed such as $Pd(OH)_2$ and ammonium formate, the nucleobase underwent double bond reduction as reported in the original synthesis.[16]

As the cleavage of the benzyl group in **8** seemed to be problematic, we decided to use a similar strategy by protecting the 2,3-*cis*-diol of 5-methyluridine with a naphthylidene acetal, which can be selectively cleaved releasing the 2′-alcohol. First, protection of the vicinal diol in 5-methyluridine with naphthaldehyde dimethyl acetal catalyzed by CSA provided a mixture of diasteroisomers at the acetal carbon atom of **9** in 85% yield (Scheme 3). Attempts to introduce a 4′-

Scheme 3. Synthesis of Dioxabicyclo Nucleoside 17[a]



[a]Reagents and conditions: (a) 2-Naphthaldehyde dimethyl acetal, CSA, 1,2-DCE; (b) $TiCl_4$, $NaBH_3CN$, MeCN; (c) TBSCl, DMAP, pyridine; (d) TFA, AcOH; (e) DMP, CH_2Cl_2; (f) 37% formaldehyde, NaOH, THF, then $NaBH_4$; (g) TrCl, DMAP, NEt_3, DMF; (h) TBDPSCl, imidazole, CH_2Cl_2, then TFA; (i) DMP, CH_2Cl_2; (j) $AlMe_3$, toluene; (k) DMP, CH_2Cl_2; (l) $LiAlH_4$, THF; (m) DMP, CH_2Cl_2; (n) MeLi, CuI, MTBE; (o) MsCl, pyridine; (p) HCl/THF/MeOH; (q) K_2CO_3, MeOH.

hydroxymethyl group at this stage, as in **1**, resulted in low yields and presented solubility issues. Reductive cleavage of the acetal at the 2′-position in **9** gave **10** in 94% yield. Double protection of the primary and secondary alcohols with TBSCl and subsequent cleavage of the 5′-*O*-silyl group gave nucleoside **11**. Following the same sequence as for the synthesis of **1** led to the bis-4′-hydroxymethyl analogue **12** in 48% yield over two steps. Selective tritylation followed by protection with TBDPSCl and a one-pot cleavage of the trityl group led to **13** in 48% yield.

The aldehyde obtained from the oxidation of **13** was treated with $AlMe_3$ to give the undesired (*S*)-isomer at the 6′-position in **14**. Therefore, it was necessary to oxidize to the corresponding ketone with DMP and reduce with $LiAlH_4$ to obtain the (*R*)-isomer **15**. Alternatively, treatment of the

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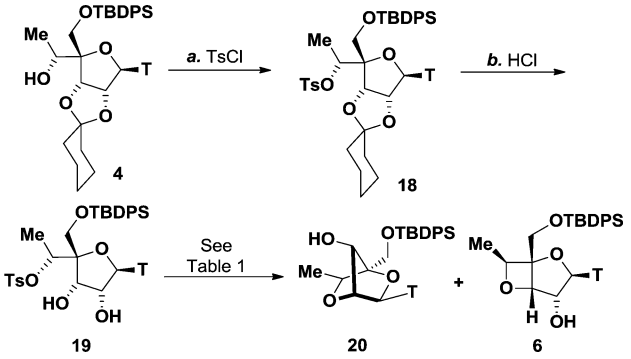
aldehyde resulting from the oxidation of **13** with MeLi/CuI in MTBE, as described in Scheme 2, led to formation of alcohol **15** in 44% yield over two steps. Mesylation and subsequent cleavage of the TBS ether in **15**, followed by treatement with K_2CO_3 in MeOH, led to the intended orthogonally protected bicyclic nucleoside (*S*)-cEt-BNA **17** in 2% overall yield over 13 steps from 5-methyluridine. The ^1H and ^{13}C NMR for compound **17** matched with the data reported by Isis Pharmaceuticals.[16]

Lastly, we decided to focus our attention on the direct cyclization of (*S*)-cEt-BNA from the corresponding unprotected 2′,3′-*cis*-diol, thereby shortening the synthetic sequence. With this objective in mind, **4** was O-tosylated to give **18** which was treated with a mixture of HCl/MeOH/THF to remove the cyclohexylidene acetal, affording diol **19** in good yield (Scheme 4). More than 40 conditions were tried to favor the formation

Scheme 4. Intramolecular Cyclization[a]



[a]Reagents and conditions: (a) TsCl, DMAP, pyridine; (b) HCl/THF/MeOH.

of the [2.2.1]dioxabicycloheptane core motif in **20** over the four-membered ring oxetane (see Supporting Information). In Table 1 are shown the best results obtained. The use of

Table 1. Optimization of the Key Cyclization To Produce 20

entry	conditions	ratio[a] of 6:20:19
1	pyridine, 80 °C, 3 days	1.0:1.7:0
2	phenanthridine (2 equiv), PhMe, 80 °C, 20 h	1.0:1.5:5.0
3	1,10-phenanthroline, (2 equiv), PhMe, 80 °C, 20 h	1.0:2.0:2.6
4	1-methyl-2-pyrrolidinone, 80 °C, 24 h	1.0:2.1:11
5	DMSO, 80 °C, 24 h	1.0:2.7:1.0
6	HMPA, 100 °C, 20 h	1.0:3.6:0
7	DMPU, 100 °C, 20 h	1.0:1.1:0
8	water 90 °C, 20 h	1.0:2.4:4.7

[a]All the ratios were measured by ^1H NMR.

pyridine showed a selectivity toward the five-membered ring, albeit requiring long reaction times to complete the reaction. Driven by the promising results obtained with pyridine, different compounds bearing the pyridine ring such as phenanthridine and 1,10-phenanthroline were screened, obtaining the best ratio in entry 3. Employing common amine bases such as DBU, NEt_3, DIPEA, imidazole, or TMP (see Supporting Information) led to low selectivity toward the desired 5-exotet cyclization product **20**.

On the basis of the moderate to low selectivities obtained with bases of different strengths, we rationalize that the sugar moiety in compound **19** is favored toward a southern type conformation in which the 3′-OH is well positioned for an S_N2 attack on the 6′-tosylate.

Measuring the $J_{1',2'}$ coupling constant between the signals of the H1′,H2′ protons for nucleoside **19** and bicyclic products **6** and **20**, it was possible to calculate the percentage of molecules in a northern type conformation (Figure 2).[28] The values

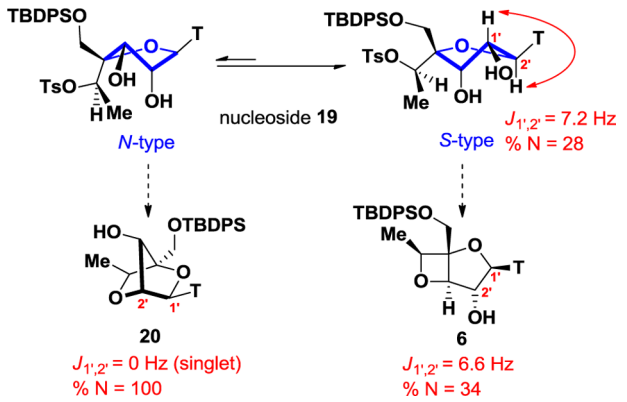


Figure 2. Intramolecular cyclization influenced by the conformation of nucleoside **19**.

obtained for nucleoside **19** and the undesired product **6** at room temperature in $CDCl_3$ are 28% and 34%, respectively. These values clearly show that the C3′-endo-C2′-exo (N-type) conformation required in **19** to favor the formation of the five-membered ring is strongly disfavored. The favorable alignment of the 3′-OH with the C6′-tosylate results in the formation of the oxetane product as major product.

In an effort to change the natural N-type conformation of the nucleoside **19**, we performed the cyclization in different polar solvents at high temperature in absence of base (Table 1, entries 4−8). Heating in nonprotic polar solvents such as DME and DMF favored the formation of the bicyclic oxetane product **6**. Better selectivity was achieved when 1-methyl-2-pyrrolidinone and DMSO were employed as solvents (Table 1, entries 4 and 5). The use of HMPA as solvent afforded a 3.6:1 ratio favoring the desired product **20** which was isolated in 50% yield. The replacement of HMPA by DMPU resulted in lower selectivity (Table 1, entry 7). Finally, reaction in water showed moderate selectivity toward the desired product but with low conversion (Table 1, entry 8).

In conclusion, an O-protected (*S*)-cEt-BNA was synthesized by three different routes, including the shortest, nine linear steps and 7% overall yield, starting from inexpensive 5-methyluridine.

EXPERIMENTAL SECTION

General Procedure. All nonaqueous reactions were run in flame-dried glassware under a positive pressure of argon, with exclusion of moisture. Anhydrous tetrahydrofuran, diethyl ether, toluene, and dichloromethane were obtained by passing these solvents through activated columns of alumina, while all other solvents were used as received from chemical suppliers. Reagents were purchased and used without further purification. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica plates that were visualized using a UV lamp (254 nm) and developed with an aqueous solution of ceric ammonium molybdate or an ethanolic solution of *p*-anisaldehyde. Flash chromatography was performed using 40−63 μm (230−400

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mesh) silica gel, and all column dimensions are reported as height × diameter in centimeters. NMR spectra were recorded at 300 or 400 MHz, calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$, δ = 7.26 ppm), and reported in parts per million relative to trimethylsilane (TMS δ = 0.00 ppm) as follows: chemical shift (multiplicity, coupling constant (Hz), integration). The following abbreviations are used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets. High resolution mass spectra (HRMS) were recorded on a TOF mass spectrometer using electrospray ionization time-of-flight reflectron experiments. Specific rotation measurements are reported in units of $deg{\cdot}cm^3{\cdot}g^{-1}{\cdot}dm^{-1}$.

*1-((3a′S,6′R,6a′R)-4′,4′-Bis(hydroxymethyl)tetrahydrospiro-[cyclohexane-1,2′-furo[3,4-d]-[1,3]dioxol]-6′-yl)-5-methylpyrimidine-2,4(1H,3H)-dione) (**1**).* Camphorsulfonic acid (1.41 g, 6.10 mmol) and cyclohexanone dimethyl acetal (18.5 mL, 0.122 mol) were added to a stirred solution of 5-methyluridine (15.7 g, 60.7 mmol) in 1,2-dichloroethane (230 mL). After refluxing for 2 h, the mixture was cooled to room temperature and diluted with dichloromethane (100 mL), and saturated sodium bicarbonate solution (100 mL) was added. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting foam was dissolved in dichloromethane (200 mL) and mixed with Dess−Martin periodinane (31.0 g, 73 mmol) and sodium bicarbonate (10 g, 12 mmol). After stirring at room temperature for 3 h, ethyl acetate (100 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and the mixture was stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined organic extracts were concentrated under reduced pressure. The residue was dissolved in THF (300 mL) and stirred with a 37% aqueous solution of formaldehyde (90 mL, 1.2 mol) and 1 M NaOH (117 mL, 117 mmol). After 12 h, the reaction mixture was cooled to 0 °C and sodium borohydride (11.5 g, 0.30 mmol) was added slowly. The cooling bath was removed, and the reaction was allowed to warm to room temperature over a 3 h period. The reaction mixture was neutralized via the addition of 1 M HCl, and the resulting solution was extracted with dichloromethane (5 × 80 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give nucleoside **1** as a white foam (14 g, 62%). ^{1}H and ^{13}C NMR data matched with previously reported data.[29]

*1-((3a′S,4′R,6′R,6a′R)-4′-(((tert-Butyldiphenylsilyl)oxy)methyl)-4′-(hydroxymethyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]-dioxol]-6′-yl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**2**).* *tert*-Butyldimethylsilyl chloride (2.86 mL, 18.9 mmol) and imidazole (1.29 g, 18.9 mmol) were added to a stirred solution of nucleoside **1** (5.37 g, 14.5 mmol) in anhydrous DMF (70 mL). After 4 h at 0 °C, the reaction mixture was warmed to room temperature and mixed with imidazole (2.00 g, 2.94 mmol) and *tert*-butyldiphenylsilyl chloride (7.6 mL, 29 mmol). After 18 h, the reaction mixture was diluted with methanol (70 mL), and then trifluoroacetic acid (11.2 mL, 65.9 mmol) was added in three portions with 30 min of difference between each one. After 48 h, the reaction mixture was neutralized by addition of saturated sodium bicarbonate solution and water (300 mL). The mixture was extracted with Et_2O/EtOAc 1:1 (4 × 50 mL), and the combined organic extracts were washed with 1 M HCl (100 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (17 × 5 cm, 3:7 EtOAc/hexanes) to give **2** (3.58 g, 40%), R_f = 0.35 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.68−7.60 (m, 4H), 7.46−7.32 (m, 6H), 7.28 (s, 1H), 6.02 (s, 1H), 4.87 (s, 2H), 4.01 (d, J = 11.2 Hz, 1H), 3.95 (d, J = 11.1 Hz, 1H), 3.82 (d, J = 12.1 Hz, 1H), 3.73 (d, J = 12.0 Hz, 1H), 2.35 (s, 1H), 1.89−1.81 (m, 2H), 1.71−1.51 (m, 9H), 1.45−1.35 (m, 2H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.4, 136.2, 135.6, 135.3, 132.9, 132.4, 130.1, 130.0, 127.9, 127.9, 115.7, 111.4, 90.4, 88.3, 84.1, 81.4, 66.2, 62.8, 36.4, 34.3, 27.1, 24.9, 24.1, 23.6, 19.4, 11.9; HRMS (ESI) calcd for $C_{33}H_{43}N_2O_7Si$ $[M + H]^+$ m/z = 607.2834, found 607.2845. From the later purification, the column was flushed with EtOAc and the extract was mixed with all the noncombined fractions. The mixture of silylated products was concentrated under reduced pressure, dissolved in THF (100 mL), and mixed with 1 M TBAF in THF (50 mL, 50 mmol). After 12 h, water (50 mL) was added and the mixture was extracted with dichloromethane (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give recovered nucleoside **1** as a white foam (1.81 g) (the yield of nucleoside **2** is 61% based on recycled starting material).

*1-((3a′S,4′S,6′R,6a′R)-4′-(((tert-Butyldiphenylsilyl)oxy)methyl)-4′-((S)-1-hydroxyethyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d]-[1,3]dioxol]-6′-yl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**3**).* Dess−Martin periodinane (0.68 g, 1.6 mmol) and sodium bicarbonate (0.5 g, 6 mmol) were added to a stirred solution of nucleoside **2** (0.75 g, 1.2 mmol) in anhydrous dichloromethane (7.0 mL). After 1 h, dichloromethane (7 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in dry toluene (6.0 mL) and, at 0 °C, mixed with 2 M $AlMe_3$ in hexanes (1.9 mL, 3.8 mmol). After 1 h, the reaction mixture was diluted with 1 M HCl, the layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3 cm, 3:7 EtOAc/hexanes) to give nucleoside **3** as a white foam (0.521 g, 68%), R_f = 0.20 (2% MeOH in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.69−7.58 (m, J = 15.4, 6.5, 1.6 Hz, 4H), 7.49−7.35 (m, 7H), 6.14 (d, J = 5.3 Hz, 1H), 4.95 (d, J = 6.3 Hz, 1H), 4.79 (dd, J = 6.3, 5.4 Hz, 1H), 4.25−4.16 (m, 1H), 4.13 (d, J = 11.2 Hz, 1H), 3.96 (d, J = 11.2 Hz, 1H), 2.72 (s, 1H), 1.92−1.23 (m, 16H), 1.13 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 150.4, 135.6, 135.4, 135.3, 133.0, 132.2, 130.4, 130.3, 128.3, 128.2, 115.9, 111.7, 89.3, 89.1, 84.1, 81.5, 68.1, 64.4, 37.0, 34.8, 27.3, 25.0, 24.2, 23.8, 19.6, 16.4, 11.93; HRMS (ESI) calcd for $C_{34}H_{45}N_2O_7Si$ $[M + H]^+$ m/z = 621.2991, found 621.3004; calcd for $C_{34}H_{44}N_2NaO_7Si$ $[M + Na]^+$ m/z = 643.2810, found 643.2820. $[\alpha]_D^{25}$ = −1 (10 mg/mL, CH_2Cl_2)

*1-((3a′S,4′S,6′R,6a′R)-4′-(((tert-Butyldiphenylsilyl)oxy)methyl)-4′-((R)-1-hydroxyethyl)tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d]-[1,3]dioxol]-6′-yl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**4**).* Dess−Martin periodinane (0.46 g, 1.1 mmol) and sodium bicarbonate (0.45 g 5.3 mmol) were added to a stirred solution of nucleoside **3** (0.52 g, 0.84 mmol) in anhydrous dichloromethane (4.5 mL). After 1 h, dichloromethane (5 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 4 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in dry THF (4.5 mL) and stirred with lithium aluminum hydride (108 mg, 2.81 mmol) at −78 °C. After 1 h, the reaction mixture was diluted with ethyl acetate (5 mL) and 1 M HCl (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 4 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3 cm, 4:6 EtOAc/hexanes) to give nucleoside **4** as a white foam (520 mg, quantitative), R_f = 0.42 (2% MeOH in dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.67−7.59 (m, J = 8.0, 7.3, 1.5 Hz, 4H), 7.48−7.33 (m, 7H), 6.12 (d, J = 5.5 Hz, 1H), 4.83 (t, J = 5.7 Hz, 1H), 4.73 (d, J = 6.0 Hz, 1H), 4.15 (q, J = 6.5 J= 6.53 Hz, 1H), 3.99 (d, J = 11.3 Hz, 1H), 3.91 (d, J = 11.3 Hz, 1H), 1.89−1.30 (m, 14H), 1.17 (d, J = 6.5 Hz, 3H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.5, 135.8, 135.6, 135.4, 132.8, 132.1, 130.4, 130.3, 128.2, 128.1, 115.4, 111.5, 89.8, 89.8, 83.7, 81.7, 69.1, 65.5, 37.1, 34.6, 27.3, 25.0, 24.1, 23.7, 19.5, 17.6, 11.9; HRMS (ESI) calcd for

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$C_{34}H_{45}N_2O_7Si$ $[M + H]^+$ m/z = 621.2991, found 621.2998; calcd for $C_{34}H_{44}N_2NaO_7Si$ $[M + Na]^+$ m/z = 643.2810, found 643.2817; $[\alpha]_D^{25}$ = −8° (10 mg/mL, CH_2Cl_2). As an alternative route to **4**, Dess–Martin periodinane (303 mg, 0.714 mmol) and sodium bicarbonate (200 mg, 2.38 mmol) were added to a stirred solution of nucleoside **2** (334 mg, 0.551 mmol) in anhydrous dichloromethane (3 mL). After 2 h, dichloromethane (10 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Methyllithium (1.6 M in diethyl ether) (3.4 mL, 5.44 mmol) was added dropwise to a 0 °C solution of copper iodide (526 mg, 2.76 mmol) in MTBE (16 mL). After 30 min, the solution of the crude aldehyde in MTBE (10 mL) was cannulized quickly to the cuprate suspension. The reaction mixture was allowed to reach room temperature in a period of 3 h, then saturated ammonium chloride (50 mL) was added and stirred for 10 min. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 × 30 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 3 cm, 4:6 EtOAc/hexanes) to give nucleoside **4** (175 mg, 51% over two steps) (38 mg of the undesired (*S*)-alcohol were isolated.)

*(R)-1-((2R,3S,4R,5R)-2-(((tert-Butyldiphenylsilyl)oxy)methyl)-3,4-dihydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-tetrahydrofuran-2-yl)ethyl Methanesulfonate (**5**).* Methanesulfonyl chloride (50 μL, 0.18 mmol) and 4-dimethylaminopyridine (10 mg, 0.082 mmol) were added to a stirred solution of nucleoside **4** (0.25 g, 0.084 mmol) in anhydrous pyridine (2 mL) at 0 °C. The reaction was stirred at room temperature for 12 h and then diluted with 1 M HCl (3 mL) and EtOAc (3 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 4 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (3:7 EtOAc/hexanes) to give the mesylate nucleoside (0.24 g, 85%), R_f = 0.60 (15 × 2.5 cm, 5% MeOH in dichlorometane). A 37% aqueous solution of HCl (1.50 mL, 17.5 mmol) was added to a stirred solution of the previous synthesized mesylate (0.15 g, 0.22 mmol) in THF (1 mL) and MeOH (2 mL). After 12 h, the reaction was neutralized via addition of saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted with dichloromethane (5 × 4 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (2:1 EtOAc/hexanes) to give nucleoside **5** as a white foam (86 mg, 63%), R_f = 0.28 (15 × 1.5 cm, 4:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 7.69–7.57 (m, 4H), 7.49–7.32 (m, 7H), 6.12 (d, J = 7.5 Hz, 1H), 5.37–5.14 (m, J = 6.4 Hz, 2H), 4.58 (dd, J = 7.6, 5.4 Hz, 1H), 4.43 (d, J = 5.3 Hz, 1H), 3.98–3.87 (m, J = 7.4 Hz, 2H), 3.62 (s, 1H), 3.01 (s, 3H), 1.40 (d, J = 6.5 Hz, 3H), 1.35 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 152.1, 136.0, 135.6, 135.3, 132.8, 131.86, 130.6, 130.3, 128.3, 128.2, 111.4, 89.6, 81.5, 74.7, 72.6, 64.1, 38.3, 29.8, 27.3, 19.6, 18.3, 11.9; HRMS (ESI) calcd for $C_{29}H_{39}N_2O_9SSi$ $[M + H]^+$ m/z = 619.2140, found 619.2151; calcd for $C_{29}H_{38}N_2NaO_9SSi$ $[M + Na]^+$ m/z = 641.1959, found 641.1972.

*1-((1S,3R,4R,5S,7S)-1-(((tert-Butyldiphenylsilyl)oxy)methyl)-4-hydroxy-7-methyl-2,6-dioxabicyclo[3.2.0]heptan-3-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**6**).* Potassium carbonate (3 mg, 0.02 mmol) was added to a stirred solution of **5** (9.2 mg, 0.014 mmol) in methanol (2 mL). After stirring at 70 °C for 24 h, the solution was concentrated under reduced pressure and the solid residue was dissolved in MeOH:CH_2Cl_2 (5%). The solution was passed through a silica gel pad and eluted with 5% MeOH:CH_2Cl_2). The obtained solution was concentrated under reduced pressure. The residue did not require further purification and provided nucleoside **6** as a white foam (7 mg, 90%), R_f = 0.21 (3:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.73–7.57 (m, 4H), 7.52–7.34 (m, 6H), 7.19 (s, 1H), 6.35 (d, J = 6.7 Hz, 1H), 4.96 (d, J = 4.8 Hz, 1H), 4.77 (q, J = 6.6 Hz, 1H), 4.14–4.03 (m, 1H), 3.96 (q, J = 11.6 Hz, 2H), 3.03 (d, J = 10.1 Hz, 1H), 1.66 (s, 3H), 1.36 (d, J = 6.7 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3, 150.8, 135.6, 135.4, 132.9, 132.3, 130.4, 130.3, 128.2, 128.1, 112.1, 89.0, 88.0, 86.4, 81.7, 76.1, 61.5, 27.0, 19.5, 18.1, 12.2; HRMS (ESI) calcd for $C_{28}H_{35}N_2O_6Si$ $[M + H]^+$ m/z = 523.2259, found 523.2252; calcd for $C_{28}H_{34}N_2NaO_6Si$ $[M + Na]^+$ m/z = 545.2078, found 545.2074.

*(1R)-1-((3aS,4R,6R,6aR)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)-6-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-phenyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)ethyl Methanesulfonate (**7**).* Camphorsulfonic acid (2 mg, 0.008 mmol) and benzaldehyde dimethyl acetal (0.1 mL, 0.6 mmol) were added to a stirred solution of **5** (38 mg, 0.062 mmol) in 1,2-dichloroethane (0.3 mL). After refluxing for 1 h, the mixture was cooled to room temperature and diluted with dichloromethane (1 mL). The crude mixture was preadsorbed on silica gel and purified by flash chromatography (14 × 1 cm, 3:7 EtOAc/hexanes) to give a mixture of isomers **7** as a white foam (36 mg, 82%), R_f = 0.46 (4:6 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.29 (m, 15H), 7.06 (d, J = 6.7 Hz, 1H), 6.19 (d, J = 4.9 Hz, 1H), 5.97 (d, J = 6.5 Hz, 1H), 5.10–4.92 (m, 2H), 4.82 (d, J = 6.1 Hz, 1H), 4.73 (d, J = 6.0 Hz, 1H), 4.07–3.92 (m, 2H), 3.55 (d, J = 4.9 Hz, 3H), 1.62 (d, 3H), 1.36 (d, J = 6.5 Hz, 3H), 1.11 (d, J = 7.2 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 137.9, 135.7, 135.7, 135.5, 135.4, 135.2, 134.9, 134.2, 132.3, 132.1, 131.7, 130.7, 130.6, 130.3, 130.2, 128.9, 128.8, 128.4, 128.3, 128.3, 128.3, 128.1, 127. 9, 127.8, 127.0, 127.0, 125.9, 125.7, 108.2, 107.9, 89.8, 84.8, 83.5, 83.5, 80.9, 80.7, 64.3, 64.2, 57.7, 38.4, 38.1, 27.3, 27.3, 19.5, 19.4, 18.2, 18.1, 13.0, 13.0; HRMS (ESI) calcd for $C_{36}H_{43}N_2O_9SSi$ $[M + H]^+$ m/z = 707.2453, found 707.2423.

*1-((1S,3R,4R,6S,7S)-7-(Benzyloxy)-1-(((tert-butyldiphenylsilyl)-oxy)methyl)-6-methyl-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**8**).* Titanium tetrachloride (28 μL, 0.25 mmol) was added dropwise to a stirred solution of sodium cyanoborohydride (16 mg, 0.25 mmol) and nucleoside **7** (36 mg, 0.051 mmol) in dry acetonitrile (0.5 mL) at 0 °C. After 1 h, the reaction mixture was diluted with saturated sodium bicarbonate (1 mL) and dichloromethane (1 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude solid was dissolved in dichloromethane and passed through a silica gel pad and eluted with 5% MeOH:CH_2Cl_2). The obtained solution was concentrated under reduced pressure. The crude solid was dissolved in MeOH (1 mL) and mixed with K_2CO_3 (6 mg, 0.04 mmol). After refluxing for 2 h, the solution was concentrated under reduced pressure and the solid residue was dissolved in 5% MeOH:CH_2Cl_2. The solution was passed through a silica gel pad and eluted with 5% MeOH:CH_2Cl_2. The obtained solution was concentrated under reduced pressure. The residue did not require further purification and provided nucleoside **8** as a white foam (23 mg, 73% over two steps), R_f = 0.48 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.74–7.65 (m, 4H), 7.49–7.26 (m, 13H), 5.64 (s, 1H), 4.67 (d, J = 11.3 Hz, 1H), 4.64 (s, 1H), 4.49 (d, J = 11.3 Hz, 1H), 4.15–3.95 (m, 4H), 1.68 (s, 3H), 1.25 (d, J = 6.6 Hz, 4H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 149.7, 136.9, 135.7, 135.5, 134.6, 132.9, 132.4, 130.2, 128.6, 128.2, 128.1, 128.0, 127.9, 110.4, 89.6, 87.4, 81.2, 72.5, 59.3, 27.0, 26.7, 19.6, 16.5, 12.4. HRMS (ESI) calcd for $C_{35}H_{41}N_2O_6Si$ $[M + H]^+$ m/z = 613.2728, found 613,2729; calcd for $C_{35}H_{40}N_2NaO_6Si$ $[M + Na]^+$ m/z = 635.2548, found 635.2549.

*1-((3aR,4R,6R,6aR)-6-(Hydroxymethyl)-2-(naphthalen-2-yl)-tetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**9**).* Naphthaldehyde dimethyl acetal (250 mg, 1.23 mmol) and camphorsulfonic acid (12 mg, 0.05 mmol) were added to a stirred solution of 5-methyluridine (120 mg, 0.465 mmol) in anhydrous 1,2-dichloroethane (2 mL). The reaction was heated to reflux for 2 h, cooled to room temperature, and mixed with solid sodium bicarbonate (50 mg). The suspension was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (15 × 1.5 cm, 7:3 EtOAc:hexanes) to give a mixture of isomers **9** as a white foam (156 mg, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 2H), 8.00–7.78 (m, 7H), 7.66–7.46 (m, 5H),

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7.16−7.07 (m, 2H), 6.27 (s, 1H), 6.17 (s, 1H), 5.69−5.62 (m, 2H), 5.33−5.27 (m, 1H), 5.26−5.13 (m, 3H), 4.50 (q, J = 3.2 Hz, 1H), 4.37 (q, J = 3.5 Hz, 1H), 4.07−3.82 (m, 3H), 3.25 (s, 2H), 1.97−1.85 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 163.9, 150.7, 150.7, 139.5, 139.0, 134.2, 134.1, 133.3, 133.2, 133.0, 132.9, 128.7, 128.7, 128.5, 128.5, 127.9, 127.9, 127.0, 126.9, 126.7, 126.6, 126.6, 126.6, 123.6, 111.6, 111.5, 108.1, 104.5, 96.5, 95.7, 86.9, 85.3, 84.2, 83.6, 81.7, 80.2, 62.9, 62.8, 51.0, 12.5, 12.4; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_6$ $[M + H]^+$ m/z = 397.1394, found 397.1395; calcd for $C_{21}H_{20}N_2NaO_6$ $[M + Na]^+$ m/z = 419.1214, found 419.1215.

*1-((2R,3R,4S,5R)-3-Hydroxy-5-(hydroxymethyl)-4-(naphthalen-2-ylmethoxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**10**).* Titanium tetrachloride (2.55 mL, 23.2 mmol) was added dropwise to a stirred solution of sodium cyanoborohydride (1.46 g, 23.2 mmol) and nucleoside **9** (1.84 g, 4.63 mmol) in dry acetonitrile (100 mL) at 0 °C. After 2 h, the reaction was diluted with saturated sodium bicarbonate (30 mL) and dichloromethane (30 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3 cm, 4:1 EtOAc/hexanes) to give nucleoside **10** as a white foam (1.74 g, 94%), R_f = 0.37 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.87−7.71 (m, 4H), 7.51−7.38 (m, 3H), 7.28 (s, 1H), 5.65 (d, J = 5.1 Hz, 1H), 4.87−4.72 (m, 2H), 4.55−4.45 (m, 1H), 4.28−4.20 (m, 1H), 4.20−4.13 (m, 1H), 3.92−3.81 (m, 1H), 3.70−3.58 (m, 1H), 3.41 (s, 1H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 151.0, 138.0, 134.6, 133.3, 133.2, 128.6, 128.0, 127.8, 127.1, 126.5, 126.3, 125.8, 111.0, 93.0, 83.4, 77.4, 73.1, 72.9, 62.2, 12.4; HRMS (ESI) calcd for $C_{21}H_{23}N_2O_6$ $[M + H]^+$ m/z = 399.1551, found 399.1555; calcd for $C_{21}H_{22}N_2NaO_6$ $[M + Na]^+$ m/z = 421.1370, found 421.1376; $[\alpha]_D^{25}$: −20 (10 mg/mL, CH_2Cl_2).

*1-((2R,3R,4R,5R)-3-((tert-Butyldimethylsilyl)oxy)-5-(hydroxymethyl)-4-(naphthalen-2-ylmethoxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**11**).* Imidazole (720 mg, 10.6 mmol) and TBSCl (1.58 g, 10.5 mmol) were added to a solution of nucleoside **10** in anhydrous DMF (12 mL). After stirring for 15 h, EtOH (10 mL) and 1 M HCl (10 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain a yellow oil. TFA (0.86 mL, 11 mmol) and 80% (w/v) AcOH (20 mL) were added to a stirred solution of the crude oil in THF (2 mL). After stirring at room temperature for 6 h, the reaction was neutralized via addition of a saturated solution of sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3 cm, 1:1 EtOAc/hexanes) to give nucleoside **11** as a white foam (1.16 g, 52% over two steps), R_f = 0.3 (1:1 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.90−7.72 (m, J = 16.4, 10.4 Hz, 4H), 7.55−7.28 (m, 4H), 5.53 (d, J = 5.6 Hz, 1H), 4.94 (d, J = 11.9 Hz, 1H), 4.82−4.61 (m, 2H), 4.33−4.21 (m, 1H), 4.10−3.99 (m, J = 11.9, 7.5 Hz, 1H), 3.97−3.86 (m, 1H), 3.74−3.60 (m,1H), 3.22 (s, 1H), 1.89 (s, 3H), 0.92 (s, 9H), 0.11 (d, J = 17.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 150.5, 139.3, 135.4, 133.4, 133.3, 128.6, 128.1, 128.0, 126.7, 126.5, 126.3, 125.8, 111.0, 95.0, 84.5, 73.2, 73.1, 62.6, 26.0, 25.9, 18.3, 12.5, −4.5, −4.8; HRMS (ESI) calcd for $C_{27}H_{37}N_2O_6Si$ $[M + H]^+$ m/z = 513.2415, found 513.2423; calcd for $C_{27}H_{36}N_2NaO_6Si$ $[M + Na]^+$ m/z = 535.2235, found 535.2241.

*1-((2R,3R,4S)-3-((tert-Butyldimethylsilyl)oxy)-5,5-bis(hydroxymethyl)-4-(naphthalen-2-ylmethoxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**12**).* Dess−Martin periodinane (1.2 g, 2.9 mmol) and sodium bicarbonate (1.02 g, 11.9 mmol) were added to a stirred solution of nucleoside **11** (1.16 g, 2.26 mmol) in anhydrous dichloromethane (12 mL) at room temperature and stirred for 1.5 h. EtOAc (10 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 8 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in THF (18 mL) and stirred with a 37% aqueous solution of formaldehyde (2.4 mL, 32 mmol) and 1 M NaOH (4.5 mL, 4.5 mmol). After 1 h, the reaction mixture was cooled to 0 °C and sodium borohydride (440 mg, 11.6 mmol) was added. The cooling bath was removed, and stirring was continued for 3 h at room temperature. The reaction mixture was neutralized via the addition of 1 M HCl, and the resulting solution was extracted with dichloromethane (5 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (4:6 EtOAc:hexanes) to give nucleoside **12** as a white foam (594 mg, 48% over two steps); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.90−7.79 (m, 3H), 7.76 (s, 1H), 7.53−7.41 (m, 3H), 7.19 (s, 1H), 5.53 (d, J = 5.4 Hz, 1H), 5.07 (d, J = 11.5 Hz, 1H), 4.98−4.89 (m, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 5.7 Hz, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.73−3.54 (m, 3H), 3.29 (s, 1H), 2.76 (s, 1H), 1.91 (s, 3H), 0.91 (s, 9H), 0.14 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 150.6, 139.8, 134.9, 133.3, 133.2, 128.7, 128.0, 127.9, 126.8, 126.5, 126.4, 125. 6, 111.2, 96.4, 88.9, 79.1, 74.5, 73.7, 64.7, 64.0, 25.8, 18.05, 12.4, −4.6, −4.8; HRMS (ESI) calcd for $C_{28}H_{38}N_2NaO_7Si$ $[M + Na]^+$ m/z = 565.2341, found 565.2354.

*1-((2R,3R,4S,5R)-3-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-5-(hydroxymethyl)-4-(naphthalen-2-ylmethoxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**13**).* Trityl chloride (594 mg, 1.65 mmol), DMAP (14 mg, 0.12 mmol), and triethylamine (0.31 mL, 2.2 mmol) were added to a stirred solution of nucleoside **12** (0.59 g, 1.1 mmol) in anhydrous DMF (5.5 mL). After stirring at room temperature for 12 h, EtOAc (5 mL) and 1 M HCl (5 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (5 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2 cm, 4:6 EtOAc/hexanes) to give 6′-*O*-trityl nucleoside as a white foam (464 mg, 70% based on recovered starting material (133 mg)), R_f = 0.72 (6:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.91−7.22 (m, 22H), 5.56 (d, J = 6.1 Hz, 1H), 4.98 (d, J = 11.5 Hz, 1H), 4.95−4.89 (m, 1H), 4.64 (d, J = 11.5 Hz, 1H), 4.22 (d, J = 5.1 Hz, 1H), 4.14 (dd, J = 12.2, 3.5 Hz, 1H), 3.79−3.70 (m, 1H), 3.67 (d, J = 10.4 Hz, 1H), 3.27 (d, J = 10.3 Hz, 1H), 3.17 (dd, J = 8.7, 3.5 Hz, 1H), 1.99 (s, 3H), 0.85 (s, 9H), 0.11 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 149.9, 143.3, 138.7, 134.8, 132.7, 132.5, 128.3, 127.6, 127.5, 127.4, 127.3, 126.6, 125.9, 125.7, 125.6, 125.2, 110.6, 93.7, 88.0, 86.4, 78.5, 77.0, 73.3, 73.2, 65.0, 64.1, 25.2, 17.5, 12.0, 5.2, 5.4. HRMS (ESI) calcd for $C_{47}H_{52}N_2NaO_7Si$ $[M + Na]^+$ m/z = 807.3436, found 807.3442. *tert*-Butyldiphenylsilyl chloride (35 μL, 0.11 mmol) and imidazole (9 mg, 0.13 mmol) were added to a stirred solution of previously synthesized trityl nucleoside (52 mg, 0.078 mmol) in anhydrous dichloromethane (1 mL). After stirring at room temperature for 36 h, the reaction mixture was cooled to 0 °C, and trifluoroacetic acid (50 μL, 0.26 mmol) was added in three portions, with 5 min difference between. After 10 min, the reaction was neutralized via addition of a saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was extracted dichloromethane (4 × 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (10 × 1 cm, 3:7 EtOAc/hexanes) to give nucleoside **13** as a white foam (35.5 mg, 69%), R_f = 0.17 (1:4 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.91−7.21 (m, 18H), 6.18 (d, J = 6.3 Hz, 1H), 5.13 (d, J = 11.7 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.59−4.51 (m, 1H), 4.30 (d, J = 5.5 Hz, 1H), 3.85 (d, J = 11.3 Hz, 1H), 3.76 (d, J = 11.3 Hz, 1H), 3.71 (s, 2H), 2.49 (s, 1H), 1.61 (s, 3H), 1.10 (s, 9H), 0.94 (s, 9H), 0.17 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 150.6, 135.9, 135.5, 135.3, 134.8, 133.3, 133.2, 132.8, 132.0, 130.2, 130.2, 128.8, 128.1, 128.1, 128.1, 127.9, 126.9, 126.5, 126.3, 125.7, 111.5, 88.4, 87.5, 78.8, 75.8, 74.4, 66.5, 63.7, 27.2, 25.7, 19.5, 18.0, 12.0, −4.5, −4.7; HRMS (ESI) calcd for $C_{44}H_{56}N_2NaO_7Si_2$ $[M + Na]^+$ m/z = 803.3518, found 803.3521; $[\alpha]_D^{25}$: +38 (10 mg/mL, CH_2Cl_2).

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*1-((2R,3R,4S,5S)-3-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-5-((S)-1-hydroxyethyl)-4-(naphthalen-2-ylmethoxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**14**).* Dess–Martin periodinane (0.26 g, 0.61 mmol) and sodium bicarbonate (0.20 g, 2.4 mmol) were added to a stirred solution of nucleoside **13** (0.34 g, 0.44 mmol) in anhydrous dichloromethane (5 mL). After stirring at room temperature for 1 h, dichloromethane (5 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in dry toluene (3.0 mL) at 0 °C and stirred with 2 M $AlMe_3$ in hexanes (0.61 mL, 1.2 mmol). After 1 h, the reaction mixture was diluted with 1 M HCl (5 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2.5 cm, 4% MeOH in dichloromethane) to give nucleoside **14** as a white foam (189 mg, 60% over two steps), R_f = 0.54 (2:3 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 7.92–7.24 (m, 18H), 6.19 (d, J = 7.2 Hz, 1H), 5.23 (d, J = 11.4 Hz, 1H), 4.59 (d, J = 11.4 Hz, 1H), 4.56–4.50 (m, 1H), 4.32 (d, J = 5.2 Hz, 1H), 4.26–4.17 (m, 1H), 4.01 (d, J = 11.3 Hz, 1H), 3.89 (d, J = 11.3 Hz, 1H), 2.64 (S, 1H), 1.62 (s, 3H), 1.15 (s, 9H), 1.01 (d, J = 6.7 Hz, 3H), 0.92 (s, 9H), 0.16 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 150.6, 135.6, 135.6, 135.4, 134.6, 133.4, 133.3, 132.9, 132.0, 130.4, 130.3, 129.2, 128.2, 128.1, 128.0, 127.3, 126.6, 126.5, 125.8, 114.4, 111.7, 88.2, 86.7, 79.2, 76.4, 74.9, 67.7, 64.3, 27.3, 25.7, 19.6, 17.9, 16.2, 12.0, −4.3, −4.8; HRMS (ESI) calcd for $C_{45}H_{58}N_2NaO_7Si_2$ $[M + Na]^+$ m/z = 817.3675, found 817.3689; $[\alpha]_D^{25}$: +14 (10 mg/mL, CH_2Cl_2).

*1-((2R,3R,4S,5S)-3-((tert-Butyldimethylsilyl)oxy)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-5-((R)-1-hydroxyethyl)-4-(naphthalen-2-ylmethoxy)tetrahydrofuran-2-yl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**15**).* Dess–Martin periodinane (92 mg, 0.21 mmol) and sodium bicarbonate (0.10 g 1.2 mmol) were added to a stirred solution of nucleoside **14** (0.13 g, 0.17 mmol) in anhydrous dichloromethane (1.0 mL). After stirring at room temperature for 1.5 h, dichloromethane (1 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in dry THF (1.0 mL) and stirred with lithium aluminum hydride (24 mg, 0.63 mmol) at −78 °C. After 1 h, the reaction was diluted with ethyl acetate (3 mL) and 1 M HCl (3 mL) and then extracted with dichloromethane (4 × 4 mL). The organic extractions were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by flash chromatography (15 × 2 cm, 3:7 EtOAc/hexanes) to give nucleoside **15** as a white foam (97 mg, 73% over two steps), R_f = 0.19 (5% acetone in dichlorometane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 11.1 Hz, 1H), 7.92–7.17 (m, 18H), 6.22 (d, J = 6.6 Hz, 1H), 5.13 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.60–4.47 (m, 1H), 4.43–4.30 (m, 1H), 4.18–4.04 (m, 1H), 3.79 (d, J = 10.9 Hz, 1H), 3.59 (d, J = 11.1 Hz, 1H), 3.31 (s, 1H), 1.64 (s, 3H), 1.16–0.98 (m, 12H), 0.91 (s, 9H), 0.12 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 150.4, 136.2, 135.6, 135.4, 134.8, 133.3, 133.2, 132.7, 132.0, 130.3, 130.27, 128.6, 128.2, 128.1, 128.08, 127.9, 126.8, 126.5, 126.3, 125.7, 111.5, 89.3, 88.9, 79.6, 75.7, 74.5, 68.6, 65.8, 27.3, 27.2, 25.7, 19.5, 18.0, 16.6, 12.0, −4.4, −4.7; HRMS (ESI) calcd for $C_{45}H_{59}N_2O_7Si_2$ $[M + H]^+$ m/z = 795.3855, found 795.3851; calcd for $C_{45}H_{58}N_2NaO_7Si_2$ $[M + Na]^+$ m/z = 817.3675, found 817.3676; $[\alpha]_D^{25}$: +30 (10 mg/mL, CH_2Cl_2). Alternatively, Dess–Martin periodinane (24 mg, 0.056 mmol) and sodium bicarbonate (20 mg, 0.24 mmol) were added to a stirred solution of nucleoside **13** (35.5 mg, 0.054 mmol) in anhydrous dichloromethane (0.5 mL). After 2 h, dichloromethane (1 mL) and a 10% (w/v) solution of $Na_2S_2O_3$ were added and stirred until a clear organic phase was obtained. The layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Methyllithium (1.6 M in diethyl ether) (0.28 mL, 0.45 mmol) was added dropwise to a 0 °C solution of copper iodide (44 mg, 0.23 mmol) in MTBE (1 mL). After 30 min, the solution of the crude aldehyde in MTBE (1 mL) was cannulized quickly to the cuprate suspension. The reaction mixture was allowed to reach room temperature in a period of 3 h, and then saturated ammonium chloride (5 mL) was added and stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (4 × 4 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography to give nucleoside **15** (16 mg, 44% over two steps).

*(R)-1-((2R,3S,4R,5R)-4-((tert-Butyldimethylsilyl)oxy)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-(naphthalen-2-ylmethoxy)tetrahydrofuran-2-yl)ethyl Methanesulfonate (**16**).* Methanesulfonyl chloride (15 μL, 0.64 mmol) and 4-dimethylaminopyridine (3 mg, 0.02 mmol) were added to a stirred solution of nucleoside **15** (97 mg, 0.12 mmol) in anhydrous pyridine (1 mL) at 0 °C. The reaction was stirred at room temperature for 12 h and then diluted with 1 M HCl (2 mL) and EtOAc (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (2 × 15 cm, 1:4 EtOAc/hexanes) to give nucleoside **16** as a white foam (78 mg, 74%), R_f = 0.89 (1:1 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.91–7.28 (m, 18H), 6.26 (d, J = 7.0 Hz, 1H), 5.20–5.08 (m, 2H), 4.69–4.60 (m, 1H), 4.54 (d, J = 11.3 Hz, 1H), 4.16 (d, J = 4.8 Hz, 1H), 3.95 (d, J = 11.5 Hz, 1H), 3.88 (d, J = 11.5 Hz, 1H), 2.94 (s, 3H), 1.64 (s, 3H), 1.22–1.11 (m, 12H), 0.90 (s, 9H), 0.14 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 150.6, 135.6, 135.5, 135.4, 134.4, 133.2, 133.2, 132.3, 131.7, 130.6, 130.5, 128.5, 128.3, 128.1, 127.9, 127.0, 126.5, 126.3, 126.0, 111.9, 87.9, 87.0, 81.0, 78.7, 75.8, 74.7, 63.9, 38.2, 27.3, 25.7, 19.6, 18.0, 17.9, 12.0, −4.4, −4.7; HRMS (ESI) calcd for $C_{46}H_{61}N_2O_9SSi_2$ $[M + H]^+$ m/z = 873.3631, found 873.3627; calcd for $C_{46}H_{60}N_2NaO_9SSi_2$ $[M + Na]^+$ m/z = 895.3450, found 895.3456; $[\alpha]_D^{25}$: −14 (10 mg/mL, CH_2Cl_2).

*1-((1S,3R,4R,6S,7S)-1-(((tert-Butyldiphenylsilyl)oxy)methyl)-6-methyl-7-(naphthalen-2-ylmethoxy)-2,5-dioxabicyclo[2.2.1]-heptan-3-yl)-5-methylpyrimidine-2,4-(1H,3H)-dione (**17**).* HCl (37% (w/v)) (0.5 mL) was added to a stirred solution of nucleoside **16** (50 mg, 0.058 mmol) in THF (0.35 mL) and MeOH (0.5 mL). After 12 h, the reaction mixture was neutralized via addition of saturated sodium bicarbonate solution. Dichloromethane (2 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (2 × 15 cm, 1:1 EtOAc/hexanes) to give 2′-OH free nucleoside (30 mg, 70%), R_f = 0.25 (1:1 EtOAc/hexanes). Potassium carbonate (30 mg, 0.21 mmol) was added to a stirred solution of nucleoside 2′-OH free nucleoside (30 mg, 0.04 mmol) in MeOH (1.5 mL). After heating to reflux for 1 h, the reaction was diluted with dichloromethane, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (8 × 1 cm, 3:7 EtOAc:hexanes) to give nucleoside **17** as a white foam (24 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.86–7.64 (m, 8H), 7.52–7.28 (m, 10H), 5.64 (s, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.70–4.62 (m, 2H), 4.16–4.06 (m, 2H), 4.01 (d, J = 12.6 Hz, 2H), 1.59 (s, 3H), 1.33–1.24 (m, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.5, 149.7, 135.7, 135.5, 134.4, 134.2, 133.2, 133.2, 132.9, 132.5, 130.2, 130.2, 128.6, 128.1, 128.0, 127.9, 127.8, 127.0, 126.6, 126.4, 125.9, 110.4, 89.6, 87.3, 81.2, 72.7, 59.3, 27.0, 19.6, 16.5, 12.3; HRMS (ESI) calcd for $C_{39}H_{42}N_2NaO_6Si$ $[M + Na]^+$ m/z = 685.2704, found 685.2706; $[\alpha]_D^{25}$: +24 (10 mg/mL, CH_2Cl_2).

*(R)-1-((3a′S,4′R,6′R,6a′R)-4′-(((tert-Butyldiphenylsilyl)oxy)-methyl)-6′-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-tetrahydrospiro[cyclohexane-1,2′-furo[3,4-d][1,3]dioxol]-4′-yl)ethyl 4-Methylbenzenesulfonate (**18**).* *p*-Toluenesulfonic chloride (270 mg,

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1.42 mmol) and 4-dimethylaminopyridine (12 mg, 0.10 mmol) were added to a stirred solution of nucleoside **4** (0.29 g, 0.46 mmol) in anhydrous pyridine (2.5 mL). The reaction mixture was stirred at 70 °C for 12 h and then diluted with 1 M HCl (10 mL) and EtOAc (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (12 × 3 cm, 4:6 EtOAc/hexanes) to give nucleoside **18** as a white foam (260 mg, 76%), R_f = 0.35 (4:6 EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.65−7.52 (m, 4H), 7.51−7.33 (m, 7H), 7.22 (d, J = 8.1 Hz, 2H), 7.16 (s, 1H), 5.51 (d, J = 5.5 Hz, 1H), 4.93−4.81 (m, 1H), 4.63 (t, J = 5.5 Hz, 1H), 4.42 (d, J = 5.5 Hz, 1H), 3.91 (s, 2H), 2.35 (s, 3H), 1.81−1.19 (m, 16H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 149.9, 144.7, 135.7, 135.4, 135.3, 134.1, 132.4, 131.9, 130.6, 130.5, 129.3, 128.3, 128.2, 128.1, 115.1, 110.8, 89.3, 88.7, 84.3, 80.9, 80.4, 64.1, 37.3, 34.9, 27.2, 24.9, 24.1, 23.7, 21.7, 19.4, 17.7, 12.0; HRMS (ESI) calcd for $C_{41}H_{51}N_2O_9SSi$ $[M + H]^+$ m/z = 775.3079, found 775.3091; calcd for $C_{41}H_{50}N_2NaO_9SSi$ $[M + Na]^+$ m/z = 797.2898, found 797.2907.

*(R)-1-((2R,3S,4R,5R)-2-(((tert-Butyldiphenylsilyl)oxy)methyl)-3,4-dihydroxy-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-tetrahydrofuran-2-yl)ethyl 4-Methylbenzenesulfonate (**19**).* HCl (37% (w/v)) (0.3 mL) was added to a stirred solution of nucleoside **18** (20 mg, 0.026 mmol) in THF (0.2 mL) and MeOH (0.15 mL). After heating at 50 °C for 9 h, the reaction mixture was cooled and neutralized via addition of saturated sodium bicarbonate. Dichloromethane (3 mL) was added, the layers were separated, and the aqueous layer was extracted with dichloromethane (4 × 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (10 × 1 cm, 6:4 EtOAc/hexanes) to give nucleoside **19** as a white foam (17 mg, 94%), R_f = 0.14 (6:4 EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.64−7.52 (m, 4H), 7.52−7.33 (m, 6H), 7.24−7.15 (m, 3H), 5.58 (d, J = 7.2 Hz, 1H), 5.09 (q, J = 6.5 Hz, 1H), 4.46−4.34 (m, 1H), 4.24 (d, J = 5.1 Hz, 1H), 3.84 (s, 2H), 3.50 (bs, 2H), 2.33 (s, 3H), 1.57 (s, 3H), 1.32 (d, J = 6.6 Hz, 3H), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 151.7, 144.4, 135.6, 135.6, 135.4, 134.7, 132.4, 131.8, 130.6, 130.4, 129.3, 128.3, 128.2, 128.1, 110.98, 90.0, 88.5, 81.2, 76.2, 72.9, 64.0, 27.1, 21.7, 19.4, 17.8, 12.2; HRMS (ESI) calcd for $C_{35}H_{43}N_2O_9SSi$ $[M + H]^+$ m/z = 695.2453, found 695.2467; calcd for $C_{35}H_{42}N_2NaO_9SSi$ $[M + Na]^+$ m/z = 717.2272, found 717.2289.

*1-((1R,3R,4R,6S,7S)-1-(((tert-Butyldiphenylsilyl)oxy)methyl)-7-hydroxy-6-methyl-2,5-dioxabiclo[2.2.1]heptan-3-yl)-5-methylpyrimidine-2,4(1H,3H)-dione (**20**).* A solution of nucleoside **19** (50 mg, 72 μmol) in HMPA (0.5 mL) was heated at 150 °C for 1 h. The mixture was allowed to cool to room temperature, diluted with water (3 mL), and extracted with Et_2O (3 × 1 mL), and the combined organic extracts were washed with water (2 × 1 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1 × 8 cm, 1:1 EtOAc:hexanes) to give nucleoside **20** as a white amorphous solid (19 mg, 50%), R_f = 0.12 (1:1 EtOAc:hexanes); ^{1}H and ^{13}C NMR data matched with previously reported data.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.79−7.68 (m, 4H), 7.52−7.35 (m, 7H), 5.62 (s, 1H), 4.47 (s, 1H), 4.20−4.09 (m, 3H), 4.01 (d, J = 12.2 Hz, 1H), 1.73 (s, 3H), 1.27 (d, J = 5.3 Hz, 3H), 1.10 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 155.2, 149.7, 148.4, 135.8, 135.6, 134.5, 132.9, 130.4, 130.3, 128.2, 77.2, 71.5, 59.3, 27.0, 22.1, 19.5, 16.7, 12.4; HRMS (ESI) calcd for $C_{28}H_{35}N_2O_6Si$ $[M + H]^+$ m/z = 523.2259, found 523.2281; calcd for $C_{28}H_{34}N_2NaO_6Si$ $[M + Na]^+$ m/z = 545.2078, found 545.2095.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra of new compounds are available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Bennett, C. F.; Swayze, E. E. *Annu. Rev. Pharmacol. Toxicol.* **2010**, *50*, 259.

(2) Monia, B. P.; Lesnik, E. A.; Gonzalez, C.; Lima, W. F.; McGee, D.; Guinosso, C. J.; Kawasaki, A. M.; Cook, P. D.; Freier, S. M. *J. Biol. Chem.* **1993**, *268*, 14514.

(3) Swayze, E. E.; Bhat, B. *Antisense drug technology: principles, strategies, and applications*, 2nd ed.; CRC Press: Boca Raton, FL, 2008.

(4) Obika, S.; Nanbu, D.; Hari, Y.; Morio, K.-i.; In, Y.; Ishida, T.; Imanishi, T. *Tetrahedron Lett.* **1997**, *38*, 8735.

(5) Koshkin, A. A.; Singh, S. K.; Nielsen, P.; Rajwanshi, V. K.; Kumar, R.; Meldgaard, M.; Olsen, C. E.; Wengel, J. *Tetrahedron* **1998**, *54*, 3607.

(6) Morita, K.; Takagi, M.; Hasegawa, C.; Kaneko, M.; Tsutsumi, S.; Sone, J.; Ishikawa, T.; Imanishi, T.; Koizumi, M. *Biorg. Med. Chem.* **2003**, *11*, 2211.

(7) Enderlin, G.; Nielsen, P. *J. Org. Chem.* **2008**, *73*, 6891.

(8) Seth, P. P.; Swayze, E. E. US Patent US7399845, 2008.

(9) Saenger, W. *Principles of Nucleic Acid Structure*; Springer: New York, 1984.

(10) For a review, see Herdewijn, P. *Liebigs Ann.* **1996**, *1996*, 1337.

(11) Swayze, E. E.; Siwkowski, A. M.; Wancewicz, E. V.; Migawa, M. T.; Wyrzykiewicz, T. K.; Hung, G.; Monia, B. P.; Bennett, C. F. *Nucleic Acids Res.* **2007**, *35*, 687.

(12) Seth, P. P.; Siwkowski, A.; Allerson, C. R.; Vasquez, G.; Lee, S.; Prakash, T. P.; Wancewicz, E. V.; Witchell, D.; Swayze, E. E. *J. Med. Chem.* **2008**, *52*, 10.

(13) Gibson, N. W. *J. R. Coll. Physicians Edinburgh* **2014**, *44*, 196.

(14) Hong, D.; Kim, Y.; Younes, A.; Nemunaitis, J.; Fowler, N.; Hsu, J.; Zhou, T.; Fayad, L.; Zhang, N.; Piha-Paul, S.; Woessner, R.; Nadella, M. V.; Lawson, D.; Reimer, C.; Jo, M.; Schmidt, J.; Xiao, X.; Greenlee, S.; Hung, G.; Yamashita, M.; Blakey, D. C.; Monia, B. P.; Macleod, A. R.; Kurzrock, R. *Cancer Res.* **2014**, *74*, LB.

(15) Burel, S. A.; Han, S.-R.; Lee, H.-S.; Norris, D. A.; Lee, B.-S.; Machemer, T.; Park, S.-Y.; Zhou, T.; He, G.; Kim, Y.; MacLeod, A. R.; Monia, B. P.; Lio, S.; Kim, T.-W.; Henry, S. P. *Nucleic Acid Ther.* **2013**, *23*, 213.

(16) Seth, P. P.; Vasquez, G.; Allerson, C. A.; Berdeja, A.; Gaus, H.; Kinberger, G. A.; Prakash, T. P.; Migawa, M. T.; Bhat, B.; Swayze, E. E. *J. Org. Chem.* **2010**, *75*, 1569.

(17) Guo, J.; Frost, J. W. *J. Am. Chem. Soc.* **2002**, *124*, 10642.

(18) Seth, P. P.; Allerson, C. R.; Østergaard, M. E.; Swayze, E. E. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 296.

(19) Seth, P. P.; Allerson, C. R.; Siwkowski, A.; Vasquez, G.; Berdeja, A.; Migawa, M. T.; Gaus, H.; Prakash, T. P.; Bhat, B.; Swayze, E. E. *J. Med. Chem.* **2010**, *53*, 8309.

(20) Koshkin, A. A. *Tetrahedron* **2006**, *62*, 5962.

(21) Hanessian, S.; Wagger, J.; Merner, B. L.; Giacometti, R. D.; Østergaard, M. E.; Swayze, E. E.; Seth, P. P. *J. Org. Chem.* **2013**, *78*, 9064.

(22) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(23) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(24) Jones, G. H.; Taniguchi, M.; Tegg, D.; Moffatt, J. G. *J. Org. Chem.* **1979**, *44*, 1309.

(25) Obika, S.; Morio, K.-i.; Nanbu, D.; Imanishi, T. *Chem. Commun.* **1997**, 1643.

(26) Obika, S.; Morio, K.-i.; Nanbu, D.; Hari, Y.; Itoh, H.; Imanishi, T. *Tetrahedron* **2002**, *58*, 3039.
(27) Obika, S.; Hari, Y.; Morio, K.-i.; Imanishi, T. *Tetrahedron Lett.* **2000**, *41*, 215.
(28) Martin, A. R.; Mohanan, K.; Luvino, D.; Floquet, N.; Baraguey, C.; Smietana, M.; Vasseur, J.-J. *Org. Biomol. Chem.* **2009**, *7*, 4369.
(29) Sato, T. H.; Kawashima, T. H.; Miwa, T. O.; Dokei, K. O.; Fujimoto, C. S. Production process of ethynylthymidine compounds from 5-methyluridine as a starting material. Patent US 0054164A1: US, 2011.