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A Constrained Tricyclic Nucleic Acid Analogue of α-L-LNA: Investigating the Effects of Dual Conformational Restriction on Duplex Thermal Stability

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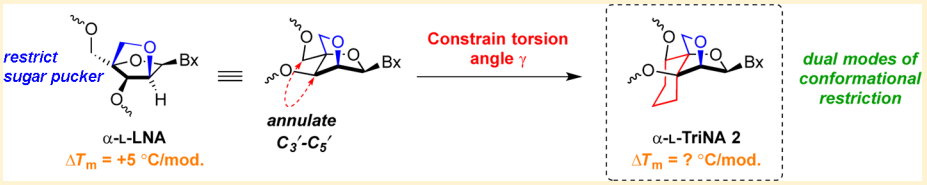
Supporting Information



ABSTRACT: A constrained tricyclic analogue of α-L-LNA (**2**), which contains dual modes of conformational restriction about the ribose sugar moiety, has been synthesized and characterized by X-ray crystallography. Thermal denaturation experiments of oligonucleotide sequences containing this tricyclic α-L-LNA analogue (α-L-TriNA 2, **5**) indicate that this modification is moderately stabilizing when paired with complementary DNA and RNA, but less stabilizing than both α-L-LNA (**2**) and α-L-TriNA 1 (**4**).

INTRODUCTION

The synthesis of modified nucleic acids that demonstrate improved target recognition and affinity, through standard Watson−Crick base pairing, is an important area of research for RNA-targeted therapeutics.[1] Antisense oligonucleotides that incorporate these synthetic nucleic acid modifications show improved duplex thermal stability versus DNA and RNA complements. The 2′,4′-bridged nucleic acid (BNA) modifications, such as LNA[2] and α-L-LNA[3] (**2**, Figure 1), are exemplary in this regard and have demonstrated marked increases in duplex thermal stability (LNA, ΔT_m = +5 °C/mod vs RNA; α-L-LNA, ΔT_m = +5 °C/mod vs RNA) when compared to unmodified or natural nucleic acids (e.g., **1**). The key structural modification in these two important nucleic acid monomers is the incorporation of a short oxamethylene bridge between the 2′- and 4′-positions, which ultimately locks the sugar pucker of the ribose moiety into an N-type, C_3'-*endo* conformation. Other important modifications to natural nucleic acids involve constraining the dihedral or torsion angles of the deoxyribose moiety.[4,5]

We recently showed that tricyclic nucleic acid analogue **4** (α-L-TriNA 1),[6] which restricts conformational mobility via spiro-annulation around the torsion angle γ in α-L-LNA, provides unprecedented improvements in oligonucleotide duplex stability in thermal denaturation (T_m) experiments (Figure 1). In the preceding article we demonstrated that constraining the torsion angle γ in a *cis*-α-L-[4.3.0]bicyclo-DNA monomer (**3**), which lacks the 2′,4′-bridging group present in α-L-LNA (**2**) and tricyclic analogue **4**, had a destabilizing effect on duplex thermal stability.[7] However, it was not clear whether the duplex destabilization observed for analogue **3** was a consequence of the steric bulk enforced by the appended six-membered ring, the conformational equilibrium of the *cis*-fused bicyclic ring system, or the absence of the 2′,4′-bridging group. To address these questions we designed α-L-TriNA 2 (**5**), a tricyclic analogue of α-L-LNA (**2**), which introduces a 2′,4′-bridging group into bicyclic analogue **3**. Introduction of this oxamethylene bridge not only locks the furanose ring in an N-type sugar pucker, but also restricts conformational mobility of the appended six-membered ring by locking the cyclohexane system in a single chair conformation (*dual conformational* restrictions). In this article we report the stereocontrolled synthesis of α-L-TriNA 2, a constrained tricyclic nucleoside modification represented by monomer **5**, as well as the duplex stabilizing properties of oligonucleotides that incorporate this modification.

At the outset of this work, there were very few reports of TriNA syntheses,[6,8] especially of systems containing a selectively protected and architecturally complex tricyclic core such as that found in **6** (Scheme 1). Molecular models indicated that formation of the 2′,4′-anhydrobridge in **6** might present a formidable synthetic challenge if carried out at a late stage in the synthesis of the designed nucleoside, given the need to invert the C_2'-OH group. However, we were also cognizant that this could be done by way of a 2,2′-

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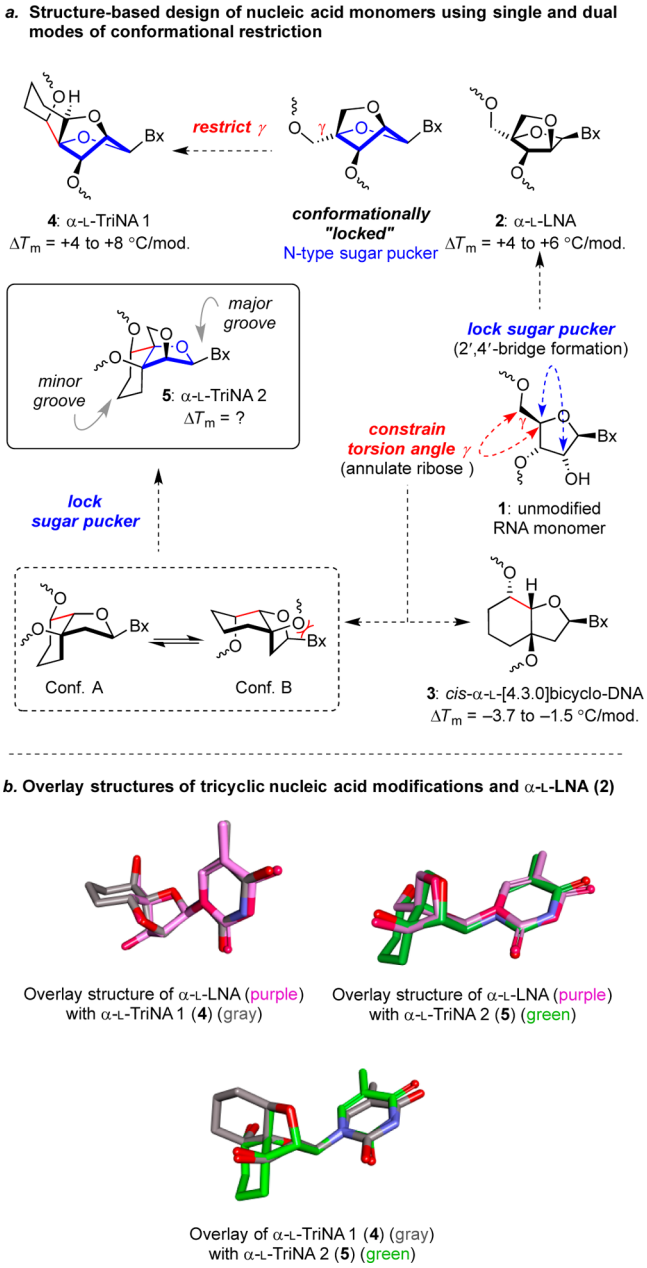
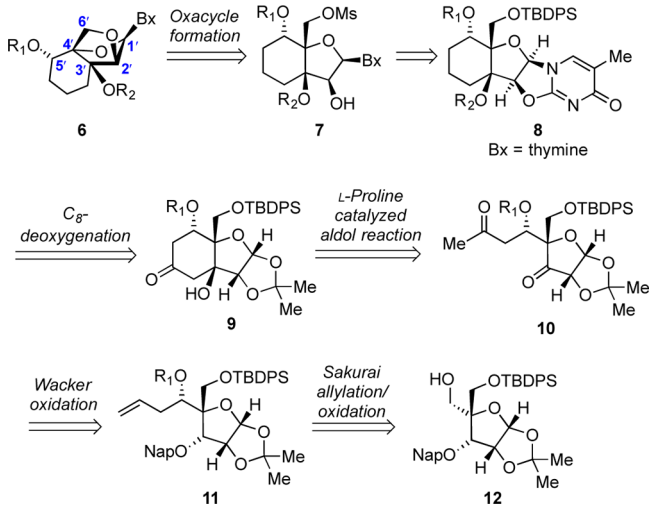


Figure 1. Rational design of tricyclic analogues of α-L-LNA (**2**).

anhydronucleoside intermediate (**8**, Scheme 1), which would ultimately be followed by intramolecular cyclization of the inverted C_2'-OH group onto a suitably activated C_5' sulfonate ester (**7**). With this strategy in mind, we focused on forming the oxabicyclic ring system of **7**, which already contained a pyrimidine nucleobase. Intramolecular aldol carbocyclization of **10** was planned to construct the six-membered carbocyclic component of the oxabicyclic ring system present in **9**. Our successful implementation of this strategy in the synthesis of *cis*-α-L-[4.3.0]bicyclo-DNA monomer **3**[7] provided the basis for following a similar approach, with the added challenge of establishing the 2′,4′-anhydrobridge present in **6** later in the synthetic sequence. The stereochemistry of the secondary alcohol on the cyclohexane ring in **11** was envisaged to originate from a stereoselective Sakurai allylation reaction on the corresponding aldehyde of **12**.[9] The retrosynthetic plan for

Scheme 1. Retrosynthetic Analysis of Tricyclic Nucleoside 6



this approach is shown in Scheme 1, with readily available bicyclic alcohol **12** as the synthetic precursor.[10]

RESULTS AND DISCUSSION

Initial forays into delineating a viable synthetic route to tricyclic nucleic acid monomer **5** were pursued for a uridine analogue of **6**. The synthesis of **6** (R_1, R_2 = H; Bx = uracil) commenced with alcohol **12** (Scheme 2), since it was available in multigram quantities from a process developed during efforts toward the synthesis of related nucleoside monomers for antisense applications.[10] Oxidation to the aldehyde, followed by a BF_3·Et_2O-mediated Sakurai allylation[9] reaction furnished (*S*)-configured homoallylic alcohol **13** in 85% yield over two steps (dr >20:1). Unfortunately, **13** proved to be resistant to standard benzylation procedures, and in all cases only starting material was recovered. In fact, the hindered nature of this secondary, neopentylic-like alcohol limited the use of protecting groups to either acetate or silyl ethers (TBS or TES). Accordingly, **13** was converted to acetate **14** to avoid compatibility issues that could arise with the introduction of a second silyl ether protecting group.

Cleavage of the isopropylidene group followed by acetylation gave a mixture of anomeric acetates that was used in a Vorbrüggen glycosylation reaction to give nucleoside **15** in 73% yield for the three-step sequence.[11] Chemoselective hydrolysis of the C_2'-OAc group followed by mesylation afforded **16** in 90% yield. Passage to tricyclic intermediate **17** was achieved through DBU-induced formation of the 2,2′-anhydronucleoside, followed by cleavage of the TBDPS ether under AcOH-buffered TBAF conditions and subsequent conversion of the resulting primary alcohol to the corresponding mesylate. Upon treatment of **17** with a 2 M solution of NaOH, formation of the 2′,4′-bridged nucleoside occurred with concomitant cleavage of the homoallylic acetate group to give **18**. Alternatively, removal of the TBDPS group and mesylation, followed by intramolecular cyclization and cleavage of the acetate also led to **18** in 65% overall yield (Scheme 2). Protection of the resulting alcohol as a TBS ether was followed by oxidative cleavage of the 2-naphthylmethyl (Nap) ether in the presence of DDQ, furnishing **19** in 76% yield. Disappointingly, the C_3'-OH group proved to be resistant to further oxidation under a variety of conditions, and, consequently, we were unable to test the proline-catalyzed intramolecular aldol cyclization. To the best

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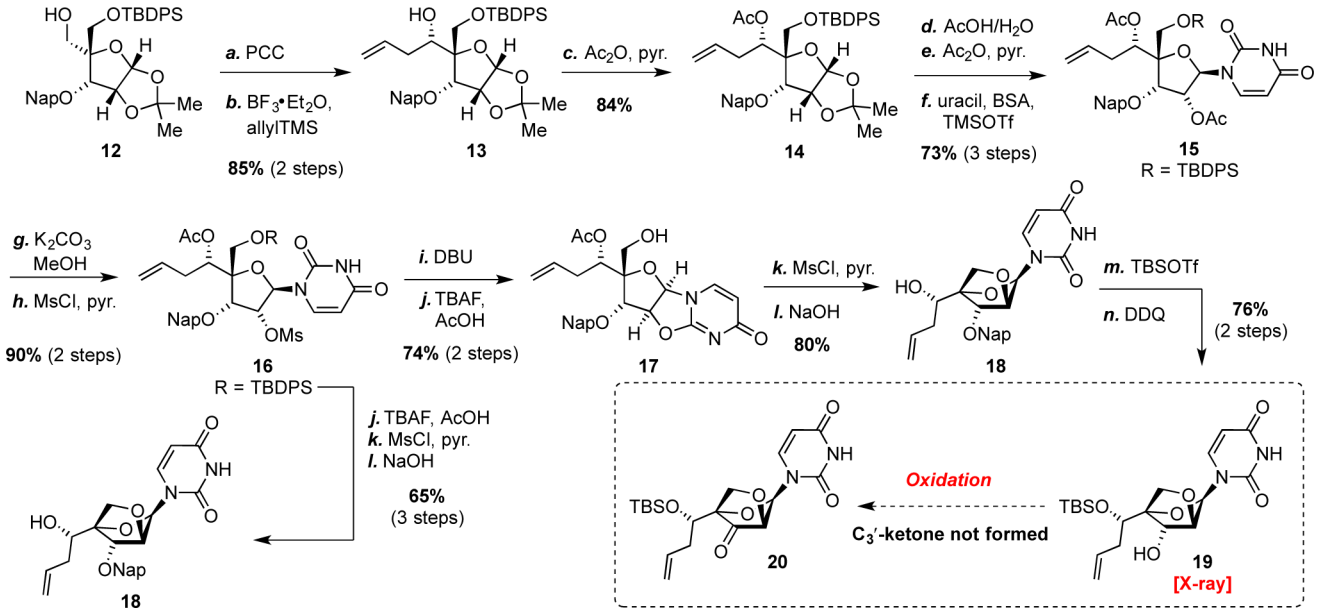
Scheme 2. Synthesis of Nucleoside 19 and Attempted Synthesis of Ketone 20[a]



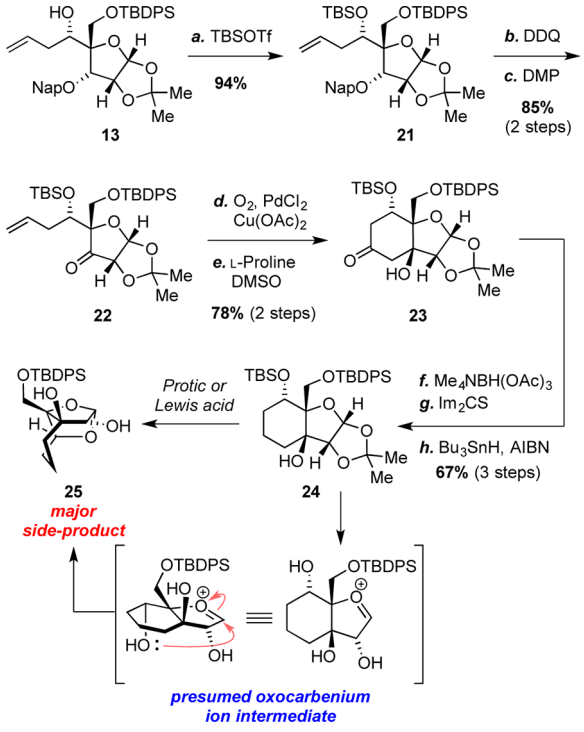
[a]Reagents and conditions: (a) PCC, CH_2Cl_2, 40 °C, 12 h; (b) $BF_3{\cdot}Et_2O$, allyltrimethylsilane, CH_2Cl_2, −40 °C, 1 h, dr >20:1; (c) Ac_2O, pyridine, 100 °C, 16 h; (d) $AcOH/H_2O$ (4:1), 90 °C, 6 h; (e) Ac_2O, pyridine, 23 °C, 12 h; (f) uracil, BSA, MeCN, 90 °C, 1 h then 0 °C, TMSOTf, 50 °C, 24 h; (g) K_2CO_3, MeOH, 23 °C, 1 h; (h) MsCl, pyridine, 23 °C, 2 h; (i) DBU, MeCN, 23 °C, 3 h; (j) TBAF, AcOH, 4 °C, 3 d; (k) MsCl, pyridine, 23 °C, 2 h; (l) NaOH, H_2O/EtOH (1:1), 90 °C, 1 h; (m) TBSOTf, CH_2Cl_2, pyridine, 23 °C, 12 h; (n) DDQ, H_2O/CH_2Cl_2 (1:9), 23 °C, 48 h.

of our knowledge, the oxidation of *endo*-disposed secondary alcohols of related 1,4-dioxa-bicyclo[2.2.1]heptane systems is unprecedented. Nevertheless, despite these shortcomings, the stereochemical outcome of the Sakurai allylation reaction was corroborated by an X-ray crystal structure of alcohol **19**.[12]

In our second approach, we once again planned to employ a proline-catalyzed intramolecular aldol reaction, which was successfully used in the synthesis of nucleoside **3** to construct the cyclohexane ring in **6**.[7] The synthesis began with the formation of TBS ether **21** (Scheme 3), which was readily converted to ketone **22** in 85% yield over two steps. Application of the Wacker oxidation gave the desired methyl ketone derivative of **22**, which underwent a smooth intramolecular aldol reaction in the presence of a catalytic amount of L-proline to furnish tricyclic ketone **23** in 78% overall yield. Reduction of the ketone[13] followed by thiocarbonyl imidazole ester formation and a Barton−McCombie deoxygenation[14] reaction led to **24**. With the carbocyclic ring of **6** now intact, the next stage in the synthetic plan called for the introduction of the thymine nucleobase. This necessitated the removal of the isopropylidene group present in **24**, which, surprisingly, proved to be incompatible with the TBS protecting group at this juncture in the synthesis. Virtually all standard and modified procedures for the acidic hydrolysis of the acetonide present in **24** led to simultaneous cleavage of the TBS ether and resulted in the formation of **25**. The formation of **25** presumably proceeds through an oxocarbenium ion intermediate that is subsequently attacked by the proximal secondary alcohol of the cyclohexane ring system (see proposed mechanism, Scheme 3).[15]

In the third and final approach (Scheme 4), we exploited differences in reactivity between the TBS and TBDPS protecting groups in the presence of TBAF. Gratifyingly, selective cleavage of the TBDPS group was possible at 0 °C in THF, furnishing the corresponding primary alcohol, which was

Scheme 3. Synthesis of Tricyclic Intermediate 24 and Undesired Acetonide Hydrolysis Side Product 25[a]



[a]Reagents and conditions: (a) TBSOTf, pyridine, CH_2Cl_2, 0 to 23 °C, 3 h; (b) DDQ, H_2O/CH_2Cl_2 (1:9), 23 °C, 6 h; (c) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 18 h; (d) O_2 (balloon), $PdCl_2$, $Cu(OAc)_2$, DMA/H_2O (7:1), 40 °C, 24 h; (e) L-proline, DMSO, 55 °C, 54 h; (f) $Me_4NBH(OAc)_3$, AcOH, MeCN, 0 to 23 °C, 7 h; (g) Im_2CS, DMAP, CH_2Cl_2, 40 °C, 19 h; (h) Bu_3SnH, AIBN, PhMe, 110 °C, 15 min.

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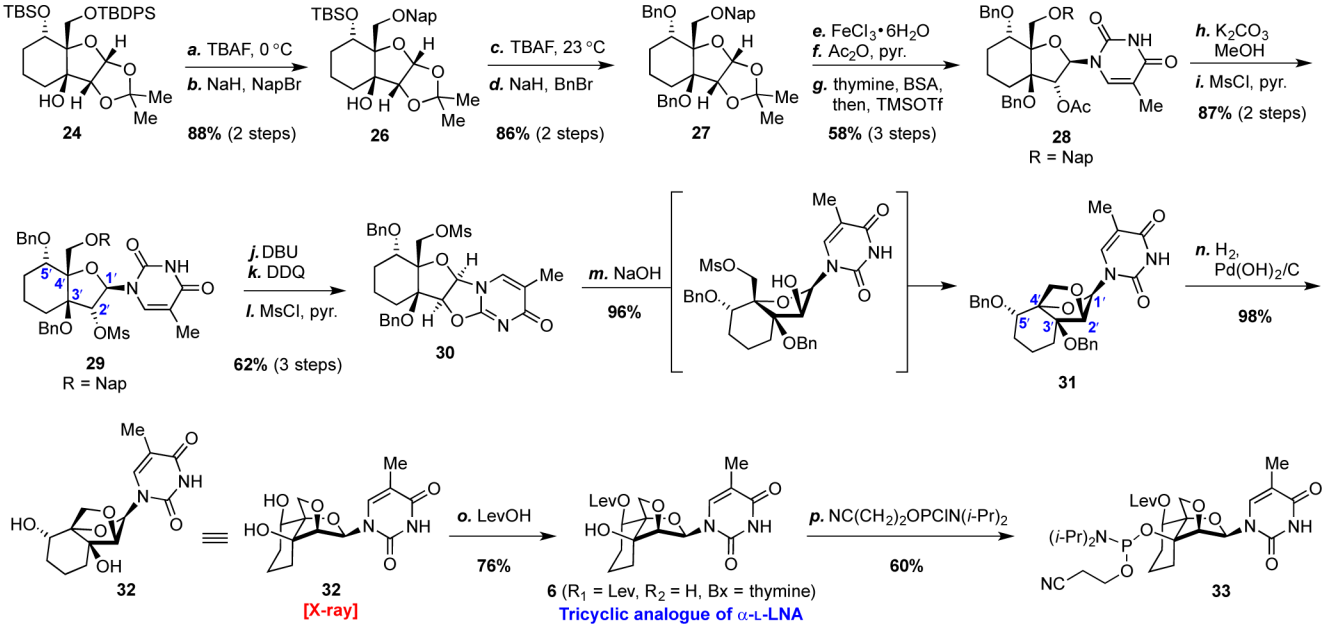
Scheme 4. Completion of the Synthesis and Preparation of Phosphoramidite 33[a]



[a]Reagents and conditions: (a) TBAF, THF, 0 °C, 1 h; (b) NaH, NapBr, TBAI, THF/DMF (1:1), 0 °C, 2 h; (c) TBAF, THF, 23 °C, 24 h; (d) NaH, BnBr, TBAI, THF/DMF (1:1), 23 °C, 3 h; (e) $FeCl_3 \cdot 6H_2O$, CH_2Cl_2, 0 to 23 °C, 1 h; (f) Ac_2O, DMAP, pyridine, CH_2Cl_2, 0 to 23 °C, 1 h; (g) BSA, thymine, 1,2-dichloroethane, 80 °C, 1 h, then TMSOTf, 0 to 80 °C, 13 h; (h) K_2CO_3, MeOH, 23 °C, 18 h; (i) MsCl, DMAP, pyridine, 0 to 23 °C, 16 h; (j) DBU, MeCN, 80 °C, 3 d; (k) DDQ, H_2O/CH_2Cl_2 (1:9), 23 °C, 3 h; (l) MsCl, DMAP, pyridine, 0 to 23 °C, 12 h; (m) 2 M NaOH, EtOH/H_2O (1:1), 100 °C, 30 min; (n) H_2, $Pd(OH)_2/C$, EtOH/MeOH (1:1), 23 °C, 15 h; (o) LevOH, Mukaiyama reagent, NEt_3, DMAP, CH_2Cl_2, 23 °C, 16 h; (p) $NC(CH_2)_2OPClN(i\text{-}Pr)_2$, *N*-methylimidazole, $EtN(i\text{-}Pr)_2$, DMF, 23 °C, 2 h.

Table 1. Sequence and Duplex Stabilizing Properties of DNA Oligonucleotides Modified with α-L-LNA (2), *cis*-α-L-[4.3.0]bc-DNA (3), α-L-TriNA 1 (4), and, α-L-TriNA 2 (5) versus Complementary DNA and RNA

ODN	mod	mass calcd	mass found	sequence (5′ to 3′)[a]	ΔT_m/mod (°C)[b] vs DNA	ΔT_m/mod (°C)[b] vs RNA
A1	DNA[c]	3633.4	3632.9	d(GCGTTTTTTGCT)	ref	ref
A2	**2**[c]	3661.4	3660.6	d(GCGTT**T**TTTGCT)	+1.4	+5.7
A3	**3**[d]	3673.4	3672.9	d(GCGTT**T**TTTGCT)	−8.8	−3.7
A4	**4**[c]	3701.5	3700.5	d(GCGTT**T**TTTGCT)	+2.6	+7.1
A5	**5**	3701.5	3700.9	d(GCGTTTTTTGCT)	−2.6	+1.2
B1	DNA[c]	3645.2	3645.5	d(CCAGTGATATGC)	ref	ref
B2	**2**[c]	3673.5	3672.6	d(CCAGTGA**T**ATGC)	+6.5	+6.3
B3	**4**[c]	3713.5	3712.7	d(CCAGTGA**T**ATGC)	+7.4	+8.3
B4	**5**	3713.5	3712.9	d(CCAGTGA**T**ATGC)	+2.3	+4.4

[a]Bold and underlined letters indicates modified nucleotide, base code: T = thymine, U = uracil, C = cytosine, A = adenine, and G = guanine. [b]T_m values were measured in 10 mM sodium phosphate buffer (pH 7.2) containing 100 mM NaCl and 0.1 mM EDTA. Sequence of DNA complements: 5′-d(AGCAAAAAACGC)-3′ for **A1**−**A5** and 5′-d(GCATATCACTGG)-3′ for **B1**−**B4**. Sequence of RNA complements: 5′-r(AGCAAAAAACGC)-3′ for **A1**−**A5** and 5′-r(GCAUAUCACUGG)-3′ for **B1**−**B4**; [c]Reference 6. [d]Reference 7.

selectively reprotected as the Nap ether to give **26** in 88% yield for the two-step sequence. Removal of the TBS ether and subsequent protection of both the secondary and tertiary alcohols as benzyl ethers afforded **27**. Having taken a somewhat circuitous (but necessary) route to a fully *O*-protected intermediate (**27**), we were able to selectively cleave the isopropylidene group without incident in the presence of $FeCl_3 \cdot 6H_2O$. Acetylation of the mixture of diasteromeric diols, followed by a Vorbrüggen glycosylation reaction gave bicyclic nucleoside **28**. Cleavage of the C_2'-OAc group and mesylation of the resulting alcohol furnished **29** in 87% yield. Three straightforward synthetic operations led to 2,2′-anhydronucleoside intermediate **30**, which upon treatment with 2 M NaOH at 100 °C underwent rapid hydrolysis of the 2,2′-anhydrouridine moiety and subsequent formation of tricyclic nucleoside **31** in 96% yield.

Hydrogenolysis afforded **32**, which could not be converted to the corresponding 4,4′-dimethoxytrityl (DMTr) derivative, presumably due to the congested tricyclic core and hindered nature of the C_5'-OH group. Fortunately, levulinyl (Lev) esters have emerged as suitable replacements of DMTr ethers,[6,16] and conversion of **32** to the corresponding Lev ester gave key nucleoside monomer **6** (R_1 = Lev, R_2 = H, Bx = thymine) for T_m studies. Single crystals of **32** suitable for X-ray diffraction analysis were obtained, which allowed us to unequivocally determine the absolute stereochemistry of the tricyclic nucleoside.[12] Furthermore, the X-ray structure of **32** shows that the ribose sugar pucker is locked in an N-type

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conformation and that the dihedral angle γ is 177° (cf., 169° for **4**).[6]

Oligonucleotide synthesis was carried out using an automated DNA synthesizer on a Unylinker-loaded polystyrene resin followed by purification using ion exchange chromatography. DNA phosphoramidites were incorporated using standard coupling, oxidation, and capping reagents. The modified phosphoramidite (**33**) was incorporated with >95% efficiency (judged by analysis of failure sequences after cleavage from the resin), using manual conditions that were previously described in detail.[6]

We measured the ability of the α-L-TriNA 2 motif (**5**, Figure 1) to stabilize oligonucleotide duplexes versus complementary DNA and RNA using two different sequences (**A** and **B**). In sequence **A**, motif **5** was incorporated into a stretch of dT nucleotides, whereas it was flanked on either side by dA nucleotides in sequence **B** (Table 1). In sequence **A**, a single incorporation of α-L-TriNA 2 (**5**) (**A5**, ΔT_m +1.2 °C/mod vs RNA and −2.6 °C/mod vs DNA) had a modest stabilizing effect on duplex thermal stability versus complementary RNA and a slightly destabilizing effect versus complementary DNA. In contrast, both α-L-LNA (**2**) (**A2**, ΔT_m +5.7 °C/mod vs RNA and +1.4 °C/mod vs DNA) and α-L-TriNA 1 (**4**) (**A4**, ΔT_m +7.1 °C/mod vs RNA and +2.6 °C/mod vs DNA) had a significantly higher stabilizing effect on duplex thermal stability. However, tricyclic analogue **5** was clearly more stabilizing than its bicyclic *cis*-α-L-[4.3.0]bicyclo-DNA counterpart (**3**) (**A3**, ΔT_m −3.7 °C/mod vs RNA and −8.8 °C/mod vs DNA), which underscores the importance of the 2′,4′-bridging group in **5**, and its contribution to improving duplex thermal stability. In sequence **B**, a single incorporation of **5** showed improved duplex thermal stability (**B4**, ΔT_m +4.4 °C/mod vs RNA and +2.3 °C/mod vs DNA) versus complementary RNA and DNA. However, the increase in T_m was still less than that observed when employing α-L-LNA (**2**) (**B2**, ΔT_m +6.5 °C/mod vs RNA and +6.3 °C/mod vs DNA) and α-L-TriNA 1 (**4**) (**B3**, ΔT_m +8.3 °C/mod vs RNA and +7.4 °C/mod vs DNA) in the same sequence. Unfortunately, a single incorporation of bicyclic analogue **3** into sequence **B** was not available for comparison. Lastly, we measured the ability of tricyclic analogue **5** to discriminate between matched and mismatched RNA complements (Table 2). We found that **5** exhibited excellent mismatch discrimination properties, which were comparable to those observed for DNA, α-L-LNA (**2**), and α-L-TriNA 1 (**4**).

Table 2. Mismatch Discrimination Properties of DNA, α-L-LNA (2), α-L-TriNA 1 (4), and α-L-TriNA 2 (5)

		ΔT_m/ mod vs RNA (°C)[a]			
		mismatch discrimination[b]		$[T_m$(mismatch) − T_m(match)]	
ODN	mod	X = A	X = G	X = C	X = U
A1	DNA	ref	−4.1	−13.0	−13.2
A2	**2**	+5.7	−4.7	−14.8	−13.5
A4	**4**	+7.1	−5.5	−16.7	−17.0
A5	**5**	+1.2	−5.7	−14.3	−12.1

[a] T_m values were measured in 10 mM sodium phosphate buffer (pH 7.2) containing 100 mM NaCl and 0.1 mM EDTA using 5′ d(GCGTT**T**TTTGCT)-3′ where the bold and underlined nucleotide indicates the site of modification; sequence of RNA complement 5′-r(AGCAAA**X**AACGC)-3′. [b] Mismatch discrimination values were calculated by subtracting the T_m measured versus the mismatched RNA complement (**X** = G, C, or U) from the T_m versus the matched RNA complement (**X** = A) for each modification.

CONCLUSIONS

This work demonstrates that incorporating a 2′,4′-anhydro-bridge into the *cis*-α-L-[4.3.0]bicyclo-DNA framework of nucleic acid analogue **3**[8] results in a significant increase in the duplex thermal stability of oligonucleotides that incorporate tricyclic analogue **5** versus those containing bicyclic analogue **3** (ΔT_m = +4.9 °C/mod vs RNA and +6.2 °C/mod vs DNA). This observation highlights the pivotal role of the 2′,4′-bridging group in restricting the conformation of the nucleoside furanose ring and consequently enhancing the thermal stability of oligonucleotide duplexes. However, the increase in duplex thermal stability produced by tricyclic nucleoside **5** was significantly lower than that seen with α-L-LNA (**2**), which suggests that the linearly annulated six-membered, carbocyclic ring in **5** has a net destabilizing contribution. This is in contrast to our previous observation with tricyclic analogue **4**, where the spiro-annulated six-membered, carbocyclic ring had an additive effect on enhancing duplex thermal stability beyond that imparted by the 2′,4′-bridging oxamethylene group.[6] Both tricyclic nucleoside modifications **4** and **5** restrict rotation around the $C_4'-C_5'$ bond (torsion angle γ) in almost the same orientation (see overlay structures, Figure 1). However, while the added bulk of the six-membered ring in **4** is expected to lie at the edge of the major groove of the modified duplex, the added bulk of the appended six-membered ring in **5** is directed into the minor groove where it could disrupt the water of hydration network around the sugar−phosphate backbone.[17] Interestingly, we have previously shown that introducing a methyl group in the (*S*)-configuration at the C_5'-position of α-L-LNA had a destabilizing effect on duplex thermal stability in comparison to α-L-LNA (**2**) and the (*R*)-5′-Me-α-L-LNA epimer.[18] The absolute stereochemistry of the 5′-carbon atom in modification **5** is also in the (*S*)-configuration. However, it remains unclear at this time as to how, or if, the configuration of the 5′-carbon atom in **5** affects duplex stability. Inverting the configuration of this stereogenic center in **5** would position the 5′-hydroxyl group in an axial orientation and drastically alter the orientation around γ from that observed in the NMR structure solution of an α-L-LNA (**2**) modified DNA/RNA duplex.[19] For these reasons, constrained nucleic acid analogues such as **4** and **5** provide additional opportunities to further probe the conformational requirements around the backbone torsion angles for efficient hybridization with complementary nucleic acids.

EXPERIMENTAL SECTION

General Procedure. All nonaqueous reactions were run in oven- (120 °C) or flame-dried glassware under a positive pressure of argon, with exclusion of moisture from reagents and glassware, using standard techniques for manipulating air-sensitive compounds, unless otherwise stated. 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 (^{1}H 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 iodine vapor, an aqueous solution of cerium ammonium molybdate, or an ethanolic solution of *p*-anisaldehyde. Flash chromatography[20] was performed using 40−63 μm (230−400 mesh) silica gel, and all column dimensions are reported as height × diameter in centimeters. NMR spectra were

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recorded at 300 or 400 MHz, calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$, δ = 7.26 ppm; CHD_2OD = 3.31 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 were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, dd = doublet of doublets, dt = doublet of triplets. High-resolution mass spectra (HRMS) were recorded on a TOF mass spectrometer using electrospray ionization time-of-flight reflectron experiments. Melting points are given as ranges and are reported in °C. Specific rotation measurements are reported in units of deg· cm^3·g^{-1}·dm^{-1}.

1,2-*O*-Isopropylidene-3-*O*-(2-naphthylmethyl)-4-*C*-(*tert*-butyldiphenylsilyl)oxymethyl-6-deoxy-6-*C*-vinyl-β-L-mannofuranose (13). PCC (5.41 g, 25.2 mmol) was added to a stirred solution of **12** (5.02 g, 8.39 mmol) in dichloromethane (60 mL). The reaction was heated to 40 °C for 13 h, cooled to room temperature, and diluted with diethyl ether (60 mL). Silica gel (*ca.* 6 g) was added, and the resulting slurry was filtered through a short pad of silica gel (4 cm), which was subsequently washed with diethyl ether (100 mL). The filtrate was evaporated under reduced pressure, and the residue was purified by flash chromatography (20 × 5 cm; 1:9 EtOAc/hexanes) to give the corresponding aldehyde (**34**) as a white solid (4.73 g, 95%): R_f = 0.32 (1:9 EtOAc/hexanes); $[\alpha]^{20}_D$ +5.4 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 7.84−7.75 (m, 4H), 7.60−7.53 (m, 4H), 7.51−7.45 (m, 3H), 7.43−7.35 (m, 2H), 7.35−7.28 (m, 4H), 5.85 (d, *J* = 3.3 Hz, 1H), 4.90 (d, *J* = 12.3 Hz, 1H), 4.78 (d, *J* = 12.3 Hz, 1H), 4.67−4.65 (m, 1H), 4.57 (d, *J* = 4.4 Hz, 1H), 3.89 (d, *J* = 11.4 Hz, 1H), 3.85 (d, *J* = 11.4 Hz, 1H), 1.64 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 135.8, 135.7, 134.6, 133.5, 133.4, 133.0, 132.8, 130.1, 130.0, 128.7, 128.1, 127.99, 127.95, 127.2, 126.5, 126.4, 125.9, 114.4, 105.1, 90.9, 79.2, 78.8, 73.2, 63.3, 26.9, 26.4, 19.4; HRMS (ESI) calcd for $C_{36}H_{40}NaO_6Si$ $[M + Na]^+$ *m*/*z* = 619.2486, found 619.2500. Boron trifluoride diethyl etherate (1.42 g, 10.0 mmol) was added to a stirred −41 °C solution of the preceding aldehyde (**34**, 3.01 g, 5.05 mmol) in dichloromethane (45 mL). After 5 min, allyltrimethylsilane (1.20 mL, 7.6 mmol) was added. The reaction was kept at −41 °C for an additional 2 h and then poured into a 0 °C saturated solution of $NaHCO_3$. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 40 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (20 × 4 cm; 8% EtOAc/hexanes) to give **13** as a white foam (2.83 g, 88%): R_f = 0.31 (1:9 EtOAc/hexanes); $[\alpha]^{20}_D$ +9.9 (*c* 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.76 (m, 4H), 7.61−7.55 (m, 2H), 7.55−7.46 (m, 5H), 7.43−7.35 (m, 2H), 7.34−7.25 (m, 4H), 5.89−5.77 (m, 2H), 5.07−4.95 (m, 2H), 4.77−4.65 (m, 3H), 4.46 (td, J_1 = 11.0, 2.1 Hz, 1H), 3.95 (d, *J* = 11.2 Hz, 1H), 3.79 (d, *J* = 11.2 Hz, 1H), 3.33 (d, *J* = 2.2 Hz, 1H), 2.51 (dd, J_1 = 14.4, 6.7 Hz, 1H), 1.95−1.82 (m, 1H), 1.63 (s, 3H), 1.38 (s, 3H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 135.8, 135.7, 134.5, 133.5, 133.4, 133.3, 133.2, 129.94, 129.85, 128.9, 128.2, 127.97, 127.95, 127.93, 127.88, 127.8, 127.5, 126.6, 126.5, 125.9, 116.4, 114.0, 104.9, 88.4, 79.4, 78.3, 73.3, 72.8, 62.7, 34.8, 27.3, 26.9, 26.7, 19.3; HRMS (ESI) calcd for $C_{39}H_{46}NaO_6Si$ $[M + Na]^+$ *m*/*z* = 661.2956, found 661.2970.

1,2-*O*-Isopropylidene-3-*O*-(2-naphthylmethyl)-4-*C*-(*tert*-butyldiphenylsilyl)oxymethyl-5-*O*-acetyl-6-deoxy-6-*C*-vinyl-β-L-mannofuranose (14). Acetic anhydride (2.86 g, 28.1 mmol) was added to a stirred solution of **13** (3.82 g, 5.98 mmol) in pyridine (12 mL), and the resulting mixture was heated to 110 °C. After 24 h, the reaction mixture was cooled to room temperature and diluted with EtOAc (50 mL), and the resulting solution was washed with 1 M HCl (4 × 100 mL). The combined aqueous phases were extracted with EtOAc (2 × 50 mL), and the organic extracts were combined, washed with 1 M HCl (100 mL) and a saturated solution of $NaHCO_3$ (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The light brown residue was purified by flash chromatography (20 × 4 cm; 1:9 EtOAc/hexanes) to give **14** (3.42 g, 84%) as a colorless oil: R_f = 0.27 (1:9 EtOAc/hexanes), $[\alpha]^{20}_D$ +15 (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.81 (m, 4H), 7.67−7.64 (m, 2H), 7.62−7.57 (m, 2H), 7.53−7.31 (m, 9H), 5.88 (d, *J* = 4.0 Hz, 1H), 5.83 (dd, *J* = 7.7, 3.0 Hz, 1H), 5.81−5.68 (m, 1H), 5.02−4.91 (m, 3H), 4.80−4.76 (m, 1H), 4.65 (d, *J* = 11.9 Hz, 1H), 4.50 (d, *J* = 5.4 Hz, 1H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.80 (d, *J* = 11.0 Hz, 1H) 2.89−2.83 (m, 1H), 2.34−2.27 (m, 1H), 1.73 (s, 3H), 1.72 (s, 3H) 1.41 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 135.8, 135.73, 135.71, 135.3, 135.2, 133.4, 133.25, 133.23, 133.1, 129.97, 129.93, 128.3, 128.1, 127.92, 127.90, 127.88, 127.0, 126.3, 126.14, 126.06, 117.0, 114.0, 105.0, 87.9, 79.5, 77.9, 73.0, 72.0, 64.3, 35.4, 26.9, 26.6, 21.1, 19.3; HRMS (ESI) calcd for $C_{41}H_{48}O_7SiNa$ $[M + Na]^+$ *m*/*z* = 703.3062, found 703.3068.

1-(2,5-*O*-Diacetyl-3-*O*-(2-naphthylmethyl)-4-*C*-(*tert*-butyldiphenylsilyl)oxymethyl-6-deoxy-6-*C*-vinyl-α-L-mannofuranosyl)uracil (15). A mixture of **14** (3.42 g, 5.02 mmol) and 4:1 AcOH/water (25 mL) was heated to 90 °C. After 3 h, the reaction mixture was poured directly into ice−water (200 mL), and the resulting solution was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were washed with water (100 mL) and a saturated solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then dissolved in pyridine (20 mL), and acetic anhydride (2.60 g, 25.1 mmol) was added. After 12 h, the reaction mixture was diluted with ethyl acetate (50 mL), and the resulting solution was washed with 1 M HCl (3 × 100 mL). The aqueous phases were combined and extracted with EtOAc (2 × 40 mL). The combined organic extracts were then washed with 1 M HCl (100 mL) and a saturated solution of $NaHCO_3$ (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 4 cm; 10% to 15% EtOAc/hexanes) to give the peracetylated product (**35**) as a light yellow oil (2.91 g, 80% over two steps). A stirred slurry of uracil (0.901 g, 8.02 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (4.08, 20.1 mmol) in acetonitrile (20 mL) was heated to 90 °C. After 1 h, the resulting mixture was cooled to 0 °C, and a solution of the preceding product (**34**, 2.91 g, 4.01 mmol) in acetonitrile (15 mL), followed by TMSOTf (1.57, 6.82 mmol), was added. The cooling bath was removed, and the reaction mixture was heated to 50 °C. After 16 h, the reaction mixture was poured into an ice-cold solution of saturated $NaHCO_3$ (40 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 4 cm; 1:2 EtOAc/hexanes) to give nucleoside **15** as a white solid (2.82 g, 91%): R_f = 0.25 (1:2 EtOAc/hexanes); mp 82−84 °C ($CHCl_3$); $[\alpha]^{20}_D$ +29 (*c* 0.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.88−7.75 (m, 3H), 7.74−7.55 (m, 6H), 7.54−7.29 (m, 10H), 6.29 (d, *J* = 5.7 Hz, 1H), 5.70−5.58 (m, 1H), 5.56−5.42 (m, 2H), 5.37 (d, *J* = 7.8 Hz, 1H), 5.01−4.87 (m, 2H), 4.69 (d, *J* = 11.1 Hz, 1H), 4.58−4.45 (m, 2H), 3.96 (d, *J* = 11.3 Hz, 1H), 3.86 (d, *J* = 11.3 Hz, 1H), 2.71−2.65 (m, 1H), 2.28−2.14 (m, 1H), 2.09 (s, 3H), 1.64 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.5, 163.2, 150.5, 139.8, 135.9, 135.6, 134.5, 134.2, 133.34, 133.28, 132.7, 131.9, 130.52, 130.45, 128.5, 128.3, 128.1, 127.9, 127.0, 126.5, 126.4, 125.9, 117.8, 103.2, 88.5, 86.6, 78.0, 77.4, 75.3, 75.0, 72.0, 64.7, 35.0, 27.23, 20.9, 19.5; HRMS (ESI) calcd for $C_{44}H_{48}N_2O_9SiNa$ $[M + Na]^+$ *m*/*z* = 799.3021, found 799.3018.

1-(2-*O*-Methanesulfonyl-3-*O*-(2-naphthylmethyl)-4-*C*-(*tert*-butyldiphenylsilyl)oxymethyl-5-*O*-acetyl-6-deoxy-6-*C*-vinyl-α-L-mannofuranosyl)uracil (16). Potassium carbonate (0.348 g, 2.52 mmol) was added to a stirred solution of **15** (1.86 g, 2.40 mmol) in methanol (40 mL). After 1 h, the reaction mixture was poured into water (40 mL) and further diluted with dichloromethane (30 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the corresponding alcohol (**36**) as a colorless oil (1.70 g, 97%). This material was used in the next step without further purification: R_f = 0.16 (1:2 EtOAc/

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hexanes); $[\alpha]^{20}_{D}$ +32 (*c* 0.22, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.87−7.81 (m, 4H), 7.64−7.60 (m, 4H), 7.50−7.31 (m, 10 H), 6.09 (d, *J* = 5.6 Hz, 1H), 5.74−5.63 (m, 1H) 5.55 (dd, *J* = 9.8, 2.6 Hz, 1H), 5.40 (dd, *J* = 8.0, 1.6 Hz, 1H), 4.99−4.93 (m, 2H), 4.88 (d, *J* = 11.4 Hz, 1H) 4.67 (d, *J* = 11.4 Hz, 1H), 4.46−4.41 (m, 1H), 4.36 (d, *J* = 6.1 Hz, 1H), 3.94−3.91 (m, 2H), 3.84 (d, *J* = 11.2 Hz, 1H), 2.77−2.68 (m, 1H), 2.34−2.23 (m, 1H), 1.75 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 140.2, 135.9, 135.6, 134.2, 133.9, 133.44, 133.36, 132.7, 132.0, 130.53, 130.47, 128.9, 128.3, 128.2, 128.0, 127.6, 126.65, 126.61, 126.1, 117.9, 103.0, 90.0, 88.3, 79.2, 77.4, 75.5, 75.2, 72.5, 65.1, 35.0, 29.9, 27.2, 21.0, 19.5; HRMS (ESI) calcd for $C_{42}H_{46}N_2O_8SiNa$ $[M + Na]^+$ *m*/*z* = 757.2916, found 757.2921. Methanesulfonyl chloride (0.357 g, 3.12 mmol) was added to a stirred solution of the preceding alcohol (**36**) in pyridine (20 mL). After 2 h, the reaction was diluted with dichloromethane (40 mL) and washed with 1 M HCl (3 × 50 mL). The aqueous phases were combined and extracted with dichloromethane (30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 3 cm; 2:3 EtOAc/hexanes) to give nucleoside **16** as a colorless oil (1.76 g, 93%): R_f = 0.29 (2:3 EtOAc/hexanes); $[\alpha]^{20}_{D}$ +41 (*c* 0.30, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.88 (d, *J* = 7.3 Hz, 2H), 7.81 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.68−7.59 (m, 2H), 7.58−7.34 (m, 6H), 6.34 (d, *J* = 6.2 Hz, 1H), 5.52−5.45 (m, 2H), 5.12−4.81 (m, 2H), 3.97 (d, *J* = 11.4 Hz, 1H), 3.86 (d, *J* = 11.4 Hz, 1H), 3.04 (s, 2H), 2.72−2.65 (m, 2H), 2.28−2.19 (m, 2H), 1.75 (s, 3H), 1.29 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.0, 150.6, 139.6, 135.9, 135.6, 134.2, 134.1, 133.3, 132.4, 131.7, 130.60, 130.55, 128.6, 128.4, 128.2, 127.9, 127.5, 126.5, 126.4, 126.1, 117.8, 103.5, 88.9, 86.2, 77.94, 77.89, 77.3, 75.2, 71.9, 65.3, 38.8, 35.0, 30.0, 27.2, 20.9, 19.5; $C_{43}H_{48}N_2O_{10}SSiNa$ $[M + Na]^+$ *m*/*z* = 835.2691, found 835.2702.

(*S*)-1-((2*S*,3*S*,3a*S*,9a*R*)-2-(Hydroxymethyl)-3-(naphthalen-2-ylmethoxy)-6-oxo-2,3,3a,9a-tetrahydro-6*H*-furo[2′,3′:4,5]-oxazolo[3,2-*a*]pyrimidin-2-yl)but-3-en-1-yl Acetate (17). DBU (0.192 g, 1.26 mmol) was added to a stirred solution of **16** (0.893 g, 1.10 mmol) in acetonitrile (25 mL). After 3 h, the reaction was poured into 1 M HCl (30 mL) and further diluted with dichloromethane (30 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the corresponding 2,2′-anhydronucleoside (**37**), which was used in the next step without further purification: R_f = 0.31 (3% MeOH/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.85−7.79 (m, 3H), 7.58−7.24 (m, 14H), 6.13 (d, *J* = 6.4 Hz, 1H), 5.99 (d, *J* = 7.5 Hz, 1H), 5.73−5.62 (m, 1H), 5.49−5.37 (m, 2H), 5.14−4.93 (m, 3H), 4.81−4.70 (m, 2H), 2.54−2.6 (m, 2H), 1.96 (s, 3H), 0.85 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.9, 159.3, 135.64, 135.60, 134.3, 133.9, 133.6, 133.43, 133.37, 132.4, 130.2, 128.9, 128.3, 128.1, 128.0, 127.9, 127.6, 126.7, 126.6, 125.7, 118.2, 110.8, 91.3, 88.7, 87.5, 84.0, 77.4, 73.8, 73.4, 63.5, 35.8, 26.7, 21.2, 19.1; HRMS (ESI) calcd for $C_{42}H_{44}N_2O_7SiNa$ $[M + Na]^+$ *m*/*z* = 739.2810, found 739.2801. A 1.0 M solution of TBAF (2.5 mL, 2.5 mmol) in THF was added to a stirred solution of acetic acid (2 mL) and the above 2,2′-anhydronucleoside (**37**, 1.26 mmol) in THF (10 mL). After 3 d, the reaction was diluted with dichloromethane (20 mL) and poured into water (20 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 2 cm; 5% MeOH/CH_2Cl_2) to give nucleoside **17** as a colorless oil (0.536 g, 74% over two steps): R_f = 0.20 (5% MeOH/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.77 (m, 4H), 7.51−7.38 (m, 3H), 7.24 (d, *J* = 6.2 Hz, 1H), 6.10 (d, *J* = 6.2 Hz, 1H), 5.95 (d, *J* = 7.1 Hz, 1H), 5.78−5.62 (m, 1H), 5.38−5.31 (m, 1H), 5.22−5.17 (m, 1H), 5.03−4.92 (m, 2H), 4.87−4.76 (m, 3H), 3.69, (d, *J* = 11.9 Hz, 1H), 3.52 (d, *J* = 11.9 Hz, 1H), 2.61−2.50 (m, 1H), 2.42−2.30 (m, 1H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 170.1, 160.2, 135.6, 134.4, 134.2, 133.2, 133.1, 128.4, 128.1, 127.8, 127.0, 126.4, 126.3, 125.8, 117.6, 109.5, 92.9, 89.7, 88.0, 85.2, 73.6, 72.5, 62.6, 35.8, 21.1; HRMS (ESI) calcd for $C_{26}H_{27}N_2O_7$ $[M + H]^+$ *m*/*z* = 479.1758, found 479.1756.

1-((1*S*,3*R*,4*S*,7*S*)-1-((*S*)-1-Hydroxybut-3-en-1-yl)-7-(naphthalen-2-ylmethoxy)-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (18). Methanesulfonyl chloride (0.171 g, 1.06 mmol) was added to a stirred solution of nucleoside **17** (0.410 g, 0.709 mmol) in pyridine. After 2 h, dichloromethane was added, and the resulting solution was washed with 1 M HCl (3 × 50 mL). The aqueous phases were combined and extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (2 × 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the corresponding mesylate (**38**, 0.464 g) as a light yellow oil, which was used in the next step without purification. A 2 M solution of NaOH (0.90 mL, 1.8 mmol) was added to a stirred 80 °C solution of the preceding mesylate (**38**, 0.464 g, 0.709 mmol) in 1:1 water/EtOH (30 mL). After 1 h, the reaction was cooled and diluted with water (30 mL), and the resulting solution was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3 cm; 3:2 EtOAc/hexanes) to give nucleoside **18** as white foam: R_f = 0.31 (3:2 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 7.89−7.81 (m, 4H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.52−7.48 (m, 3H), 6.27 (s, 1H), 5.92−5.81 (m, 1H), 5.74 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.22 (s, 1H), 5.19−5.16 (m, 1H), 4.92 (d, *J* = 12.1 Hz, 1H), 4.85, (d, *J* = 12.0 Hz, 1H), 4.50 (dd, *J* = 2.4, 0.9 Hz, 1H), 4.39, (d, *J* = 2.4 Hz, 1H), 4.14−4.09 (m, 2H), 3.89 (d, *J* = 8.8 Hz, 1H), 2.67−2.59 (m, 1H), 2.22−2.11 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.4, 140.3, 134.8, 134.3, 133.44, 133.39, 128.9, 128.2, 128.0, 127.4, 126.53, 126.48, 126.0, 117.9, 101.4, 91.2, 90.5, 81.7, 75.5, 73.4, 71.9, 67.1, 38.4, 26.0, 18.2, −3.7, −4.7; HRMS (ESI) calcd for $C_{24}H_{24}N_2O_6Na$ $[M + Na]^+$ *m*/*z* = 459.1527, found 459.1532.

1-((1*R*,3*R*,4*S*,7*S*)-1-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)but-3-en-1-yl)-7-hydroxy-2,5-dioxabicyclo[2.2.1]heptan-3-yl)-pyrimidine-2,4(1*H*,3*H*)-dione (19). TBSOTf (0.740 mmol) was added to a stirred 0 °C solution of pyridine (0.058 g, 0.74 mmol) and **18** (0.215 g, 0.493 mmol) in dichloromethane (10 mL). The cooling bath was removed, and the reaction was allowed to warm to room temperature. After 12 h, 1 M HCl (20 mL) was added, and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 2 cm; 2:3 EtOAc/hexanes) to give the corresponding TBS ether (**39**) as a colorless oil: R_f = 0.29 (2:3 EtOAc/hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.89−7.81 (m, 4H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.52−7.48 (m, 3H), 6.18 (s, 1H), 5.95−5.84 (m, 1H), 5.74 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.20−5.12 (m, 2H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.52 (dd, *J* = 2.2, 0.9 Hz, 1H), 4.35−4.31, (m, 2H), 4.15−4.11 (m, 2H), 3.99 (d, *J* = 8.8 Hz, 1H), 2.13−2.07 (m, 1H), 1.98−1.91 (m, 1H), 0.90 (s, 9H), 0.11 (s, 6H); 13C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.4, 134.8, 134.3, 133.44, 133.39, 128.9, 128.2, 128.0, 127.4, 126.53, 126.48, 126.0, 117.9, 101.4, 91.2, 90.5, 81.7, 75.5, 73.4, 71.9, 67.2, 38.4, 26.0, 18.2, −3.7, −4.7; HRMS (ESI) calcd for $C_{30}H_{38}N_2O_6SiNa$ $[M + Na]^+$ *m*/*z* = 573.2391, found 573.2399. DDQ (0.177 g, 0.781 mmol) was added to a vigorously stirred solution of the preceding TBS ether (**39**, 0.195 g, 0.355 mmol) in 9:1 dichloromethane/water (8 mL). After 48 h, the reaction mixture was poured into a 10% solution of $NaHSO_3$ (20 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 2 cm; 3:2 EtOAc/hexanes) to give nucleoside **19** as a white solid (0.120 g, 83%): R_f = 0.32 (3:2 EtOAc/hexanes);

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mp 81−83 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 6.24 (s, 1H), 6.02−5.77 (m, 1H), 5.74 (d, J = 7.8 Hz, 1H), 5.22−5.06 (m, 2H), 4.53−4.48 (m, 2H), 4.25 (dd, J = 14.5, 9.4 Hz, 1H), 4.18 (br s, 1H), 4.08 (d, J = 8.7 Hz, 1H), 3.90 (d, J = 8.7 Hz, 1H), 2.55−2.42 (m, 1H), 2.39−2.24 (m, 1H), 0.90 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 150.8, 140.4, 134.3, 118.2, 101.5, 91.0, 90.8, 77.6, 75.4, 72.4, 68.3, 38.6, 26.0, 18.2, −4.2, −4.7; HRMS (ESI) calcd for $C_{19}H_{30}N_2O_6SiNa$ [M + Na]$^+$ m/z = 433.1765, found 433.1758.

1,2-*O*-Isopropylidene-3-*O*-(2-naphthylmethyl)-4-*C*-(*tert*-butyldiphenylsilyl)oxymethyl-5-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-6-*C*-vinyl-*β*-L-mannofuranose (21). Pyridine (0.982 g, 12.4 mmol) and TBSOTf (1.61 g, 6.10 mmol) were added to a stirred 0 °C solution of **13** (2.60 g, 4.08 mmol) in dichloromethane (50 mL). The cooling bath was removed, and the reaction was allowed to warm to room temperature. After 3 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (70 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 50 mL), and the organic extracts were combined and washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 4 cm; 5% EtOAc/hexanes) to give **21** as a colorless oil (3.01 g, 98%): R_f = 0.56 (10% EtOAc/hexanes); $[\alpha]^{20}_D$ +7.7 (c 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.79 (m, 4H), 7.66−7.58 (m, 4H), 7.57−7.53 (m, 1H), 7.52−7.46 (m, 2H), 7.45−7.39 (m, 2H), 7.38−7.32 (m, 4H), 6.02 (d, J = 4.1 Hz, 1H), 5.91−5.78 (m, 1H), 5.06 (d, J = 12.0 Hz, 1H), 5.04 (br d, J = 16.8 Hz, 1H), 4.90 (br d, J = 10.1 Hz, 1H), 4.85 (dd, J = 5.2 Hz, 4.4 Hz, 1H), 4.67 (d, J = 12.0 Hz, 1H), 4.56 (dd, J = 5.6 Hz, 4.1 Hz, 1H), 4.38 (d, J = 5.6 Hz, 1H), 3.92 (d, J = 11.1 Hz, 1H), 3.79 (d, J = 11.1 Hz, 1H), 2.60−2.68 (m, 1H), 2.38−2.49 (m, 1H), 1.62 (s, 3H), 1.41 (s, 3H), 0.96 (s, 9H), 0.70 (s, 9H), −0.07 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 135.8, 135.7, 133.4, 133.3, 133.19, 133.15, 129.9, 129.8, 128.2, 128.1, 127.94, 127.90, 126.9, 126.3, 126.0, 116.7, 113.9, 105.6, 91.2, 81.0, 78.1, 77.4, 72.5, 72.0, 66.6, 38.6, 27.4, 27.3, 27.0, 26.1, 25.9, 19.3, 18.3, −3.5, −4.6; HRMS (ESI) calcd for $C_{45}H_{60}NaO_6Si_2$ [M + Na]$^+$ m/z = 775.3821, found 775.3821.

1,2-*O*-Isopropylidene-3-keto-4-*C*-(*tert*-butyldiphenylsilyl)-oxymethyl-5-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-6-*C*-vinyl-*β*-L-mannofuranose (22). DDQ (1.81 g, 7.97 mmol) was added and to a vigorously stirred solution of **21** (3.02 g, 4.01 mmol) in 9:1 dichloromethane/water (70 mL). After 6 h, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (100 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 3 cm; 2% EtOAc/hexanes) to give the corresponding alcohol (**40**) as a colorless oil (2.14 g, 88%): R_f = 0.62 (5% EtOAc/hexanes); $[\alpha]^{20}_D$ +39 (c 0.070, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H) 7.46−7.34 (m, 6H), 6.14 (d, J = 4.5 Hz, 1H), 5.85−5.70 (m, 1H), 5.00−4.87 (m, 2H), 4.91 (br d, J = 10.1 Hz, 1H), 4.30 (dd, J = 7.6 Hz, 3.4 Hz, 1H), 4.23 (dd, J = 6.4 Hz, 4.1 Hz, 1H), 3.91 (d, J = 10.9 Hz, 1H), 3.82 (d, J = 10.9 Hz, 1H), 2.92 (d, J = 4.0 Hz, 1H), 2.53−2.45 (m, 1H), 2.09−1.99 (m, 1H), 1.60 (s, 3H), 1.44 (s, 3H), 1.05 (s, 9H), 0.74 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8 135.7, 132.8, 130.1, 130.0, 128.1, 116.7, 114.8, 106.4, 94.1, 82.4, 72.0, 70.6, 67.3, 37.8, 27.9, 27.4, 27.2, 26.2, 19.3, 18.4, −3.9, −4.4; HRMS (ESI) calcd for $C_{34}H_{52}NaO_6Si_2$ [M + Na]$^+$ m/z = 635.3195, found 635.3204. Dess−Martin periodinane (2.34 g, 5.52 mmol) was added to a stirred slurry of $NaHCO_3$ (0.51 g, 5.9 mmol) and the preceding alcohol (**40**, 2.23 g, 3.52 mmol) in dichloromethane (55 mL). After 18 h, the reaction mixture was filtered through a pad of silica gel (6 × 2.5 cm), which was washed with dichloromethane (50 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (15 × 3 cm; 3% EtOAc/hexanes) to give **22** as a colorless oil (2.18 g, 97%): R_f = 0.61 (5% EtOAc/hexanes); $[\alpha]^{20}_D$ +25 (c 0.050, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.61 (m, 2H), 7.58−7.53 (m, 2H), 7.45−7.32 (m, 6H), 6.29 (d, J = 4.2 Hz, 1H), 5.03−4.97 (m, 1H), 4.97−4.92 (m, 1H), 4.42 (d, J = 4.2 Hz, 1H), 3.92 (dd, J = 8.0, 4.2 Hz, 1H), 3.85 (d, J = 10.4 Hz, 1H), 3.82 (d, J = 10.4 Hz, 1H), 2.39−2.22 (m, 2H), 1.55 (s, 3H), 1.38 (s, 3H), 0.99 (s, 9H), 0.69 (s, 9H), −0.09 (s, 3H), −0.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 135.8, 135.7, 132.5, 132.3, 130.14, 130.09, 128.1, 117.6, 115.3, 103.1, 93.3, 78.1, 73.9, 68.1, 38.5, 27.1, 27.0, 26.9, 26.0, 19.3, 18.2, −3.3, −4.6; HRMS (ESI) calcd for $C_{34}H_{50}NaO_6Si_2$ [M + Na]$^+$ m/z = 633.3038, found 633.3059.

(3a*R*,4a*S*,5*S*,8a*R*,8b*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-8a-hydroxy-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*b*]benzofuran-7(4a*H*)-one (23). $PdCl_2$ (0.065 g, 0.37 mmol) and $Cu(OAc)_2$ (0.134 g, 0.738 mmol) were added to a stirred 40 °C solution of **22** (2.23 g, 3.66 mmol) in 7:1 *N*,*N*-dimethylacetamide/water (45 mL). The reaction mixture was purged with and maintained under an atmosphere of oxygen gas (via an oxygen-filled balloon) for 24 h, at which point it was filtered through a pad of Celite and washed with diethyl ether (100 mL). The filtrate was then washed with a saturated solution of $NaHCO_3$ (200 mL), the layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 3 cm; 5% EtOAc/hexanes) to give the corresponding ketone (**41**) as a light yellow oil (2.18 g, 95%): R_f = 0.52 (10% EtOAc/hexanes); $[\alpha]^{20}_D$ +27 (c 0.090, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.63 (m, 2H), 7.60−7.56 (m, 2H), 7.46−7.33 (m, 6H), 6.21 (d, J = 4.2 Hz, 1H), 4.56 (dd, J = 7.2, 2.8 Hz, 1H), 4.41 (d, J = 4.2 Hz, 1H), 3.98 (d, J = 10.5 Hz, 1H), 3.74 (d, J = 10.5 Hz, 1H), 2.73 (dd, J = 18.0, 2.8 Hz, 1H), 2.56 (dd, J = 18.0, 7.5 Hz, 1H), 2.08 (s, 3H), 1.59 (s, 3H), 1.38 (s, 3H), 0.99 (s, 9H), 0.68 (s, 9H), −0.09 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 205.7, 135.8, 135.6, 132.6, 132.2, 130.2, 130.10, 128.1, 115.3, 102.8, 91.4, 78.2, 69.5, 66.7, 48.0, 27.2, 26.9, 26.8, 26.1, 19.2, 18.2, −3.3, −4.6; HRMS (ESI) calcd for $C_{34}H_{50}NaO_7Si_2$ [M + Na]$^+$ m/z = 649.2987, found 649.3001. L-Proline (0.116 g, 1.0 mmol) was added to a stirred 55 °C solution of the preceding ketone (**41**, 2.11 g, 3.35 mmol) in DMSO (90 mL). After 54 h, the reaction mixture was cooled to room temperature and poured into a saturated solution of $NaHCO_3$ (200 mL), and the resulting mixture was extracted with EtOAc (4 × 100 mL). The combined organic extracts were washed with water (2 × 200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (22 × 3 cm; 10% EtOAc/hexanes) to give the preceding ketone starting material (**41**, 0.155 g, 7%) and **23** (1.72 g, 82%) as a colorless solid: R_f = 0.25 (1:9 EtOAc/hexanes); mp 40−43 °C; $[\alpha]^{20}_D$ +52 (c 0.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 2H), 7.64−7.60 (m, 2H), 7.48−7.36 (m, 6H), 6.19 (d, J = 3.9 Hz, 1H), 4.62 (s, 1H), 4.61 (d, J = 3.9 Hz, 1H), 4.07 (d, J = 10.8 Hz, 1H), 3.89 (dd, J = 9.9, 3.9 Hz, 1H), 3.76 (d, J = 10.8 Hz, 1H), 2.70 (dd, J = 18.2, 9.9 Hz, 1H), 2.38 (d, J = 16.3 Hz, 1H), 2.34 (dd, J = 18.2, 3.8 Hz, 1H), 1.49 (s, 3H), 1.29 (s, 3H), 1.09 (s, 9H), 0.69 (s, 9H), −0.09 (s, 3H), −0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 135.7, 135.6, 131.6, 131.3, 130.6, 130.5, 128.4, 128.3, 114.6, 104.0, 91.2, 90.8, 80.7, 69.1, 68.0, 46.5, 43.0, 27.2, 26.7, 25.8, 19.2, 18.2, −4.4, −4.8; HRMS (ESI) calcd for $C_{34}H_{50}NaO_7Si_2$ [M + Na]$^+$ m/z = 649.2987, found 649.3002.

(3a*R*,4a*S*,5*S*,8a*R*,8b*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4a-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-*b*]benzofuran-8a(4a*H*)-ol (24). Acetic acid (1.11 mL, 19.4 mmol) was added to a stirred 0 °C slurry of tetramethylammonium triacetoxyborohydride (2.55 g, 9.69 mmol) in MeCN (45 mL). After 15 min, a solution of **23** (1.21 g, 1.93 mmol) in MeCN (80 mL) was added. The cooling bath was removed, and the reaction was allowed to warm to room temperature. After 7 h, the reaction mixture poured into water (200 mL), and the resulting solution was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (2 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (3:7 EtOAc/hexanes) to give the corresponding alcohol (**42**) as a white solid (1.13 g, 93%): R_f = 0.20 (3:7 EtOAc/

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hexanes); mp 39−42 °C; $[\alpha]^{20}_{D}$ +33 (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.61 (m, 4H), 7.45−7.32 (m, 6H), 6.14 (d, *J* = 4.8 Hz, 1H), 4.85 (d, *J* = 4.8 Hz, 1H), 3.97−3.88 (m, 2H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.57 (dd, *J* = 9.7 Hz, 3.6 Hz, 1H), 3.44 (s, 1H), 2.34−2.28 (m, 1H), 2.11 (dd, J_1 = 14.8 Hz, 6.0 Hz, 1H), 2.00−1.80 (m, 3H), 1.60 (s, 3H), 1.31 (s, 3H), 1.08 (s, 9H), 0.72 (s, 9H), −0.06 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.7, 132.1, 131.9, 130.4, 130.2, 128.2, 114.2, 104.1, 90.8, 90.1, 80.9, 69.4, 68.2, 65.1, 39.66, 37.74, 27.1, 26.9, 26.6, 19.2, 18.2, −4.3, −4.6; HRMS (ESIMS) calcd for $C_{34}H_{52}NaO_7Si_2$ $[M + Na]^+$ *m*/*z* = 651.3144, found 651.3172. DMAP (0.024 g, 0.20 mmol) and 1,1′-thiocarbonyldiimidazole (0.892 g, 4.51 mmol) were added to a stirred solution of the preceding alcohol (**42**, 2.41 g, 3.83 mmol) in dichloromethane (125 mL). The reaction mixture was then heated to 40 °C for 19 h, cooled to room temperature, and poured into a 0.5 M solution of HCl (200 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with with a saturated solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (3:7 EtOAc/hexanes) to give the corresponding thioimidazole carbamate (**43**) as a white solid (2.35 g, 83%): R_f = 0.23 (1:2 EtOAc/hexanes); mp 88−90 °C; $[\alpha]^{20}_{D}$ +23 (*c* 0.070, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.72−7.64 (m, 4H), 7.59 (s, 1H), 7.47−7.35 (m, 6H), 7.01 (s, 1H), 6.19 (d, *J* = 5.1 Hz, 1H), 5.74−5.64 (m, 1H), 4.99 (d, *J* = 5.1 Hz, 1H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.73 (d, *J* = 11.0 Hz, 1H), 3.65 (dd, *J* = 8.6 Hz, 3.6 Hz, 1H), 3.56 (s, 1H), 2.33 (s, 1H), 2.30 (s, 1H), 2.20−2.12 (m, 1H), 2.11−2.01 (m, 1H), 1.57 (s, 3H), 1.32 (s, 3H), 1.09 (s, 9H), 0.73 (s, 9H), −0.07 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 137.1, 135.8, 135.7, 132.1, 131.9, 130.8, 130.4, 130.3, 128.3, 118.0, 114.2, 104.3, 90.8, 89.8, 80.4, 77.4, 68.6, 68.1, 35.0, 34.5, 27.1, 26.6, 19.2, 18.2, −4.4, −4.7; HRMS (ESIMS): calcd for $C_{38}H_{54}N_2O_7SSi_2$ $[M + H]^+$ = 739.3263, found 739.3274. A suspension of Bu_3SnH (6.49 mL, 24.5 mmol) and AIBN (0.050 mg, 0.31 mmol) in toluene (10 mL) was added dropwise, via a syringe, to a stirred 110 °C solution of the preceding thioimidazole carbamate (**43**, 2.26 g, 3.10 mmol) in toluene (175 mL). After 15 min, from the start of the addition, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (20 × 3 cm; 5−10% EtOAc/hexanes) to give **24** as a colorless oil (1.65 g, 87%): R_f = 0.66 (15% EtOAc/hexanes); $[\alpha]^{20}_{D}$ +37 (*c* 0.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.62 (m, 4H), 7.45−7.35 (m, 6H), 6.13 (d, *J* = 5.0 Hz, 1H), 4.90 (d, *J* = 5.0 Hz, 1H), 4.06 (d, *J* = 10.9 Hz, 1H), 3.72 (d, *J* = 10.9 Hz, 1H), 3.60 (dd, *J* = 10.0 Hz, 5.2 Hz, 1H), 3.00 (s, 1H), 2.03−1.94 (m, 1H), 1.77−1.44 (m, 8H), 1.29 (s, 3H), 1.09 (s, 9H), 0.66 (s, 9H), −0.11 (s, 3H), −0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.7, 132.3, 132.2, 130.2, 130.1, 128.1, 113.7, 104.0, 92.0, 90.1, 80.6, 70.7, 68.6, 29.9, 28.4, 27.2, 26.8, 26.2, 19.2, 18.0, −3.9, −4.9; HRMS (ESI) calcd for $C_{34}H_{52}NaO_6Si_2$ $[M + Na]^+$ *m*/*z* = 635.3195, found 635.3214.

(3a*R*,4a*S*,5*S*,8a*R*,8b*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,2-dimethyl-4a-((naphthalen-2-ylmethoxy)methyl)hexahydro[1,3]dioxolo[4,5-*b*]benzofuran-8a(4a*H*)-ol (26). A 1.0 M solution of TBAF (3.23 mL, 3.23 mmol) in THF was added to a stirred 0 °C solution of **24** (1.72 g, 2.81 mmol) in THF (50 mL). After 1 h, dichloromethane (30 mL) and water (40 mL) were added. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 3 cm; 35% EtOAc/hexanes) to give the corresponding alcohol (**44**) as a colorless oil (0.97 g, 92%): R_f = 0.33 (2:3 EtOAc/hexanes); $[\alpha]^{20}_{D}$ +23 (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (d, *J* = 4.7 Hz, 1H), 4.77 (d, *J* = 4.7 Hz, 1H), 3.95−3.85 (m, 1H), 3.83−3.74 (m, 2H), 3.35−3.25 (m, 1H), 1.90−1.82 (m, 1H), 1.72−1.60 (m, 3H), 1.50 (s, 3H), 1.52−1.42 (m, 2H), 1.27 (s, 3H), 0.83 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.3, 103.4, 89.6, 89.3, 81.1, 70.3, 65.0, 30.7, 29.8, 28.8, 26.8, 26.1, 26.0, 18.5, 18.2, −4.1, −4.7; HRMS (ESI) calcd for $C_{18}H_{34}NaO_6Si$ $[M + Na]^+$ *m*/*z* = 397.2017, found 397.2010. Sodium hydride (60% dispersion in mineral oil, 0.101 g, 2.50 mmol), 2-(bromomethyl)naphthalene (0.568 g, 2.57 mmol), and tetrabutylammonium iodide (0.432 g, 1.16 mmol) were added sequentially to a stirred 0 °C solution of the preceding alcohol (**44**, 0.875 g, 2.34 mmol) in 1:1 DMF/THF (32 mL). After 2 h, methanol (7 mL) was added, and the resulting mixture was further diluted with dichloromethane (30 mL) and water (30 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (2 × 40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 3 cm; 1:9 EtOAc/hexanes) to give **26** as a colorless oil (1.15 g, 96%): R_f = 0.17 (1:9 EtOAc/hexanes); $[\alpha]^{20}_{D}$ +16 (*c* 0.050, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.79 (m, 3H), 7.74 (s, 1H), 7.52−7.45 (m, 2H), 7.42 (br d, *J* = 8.3 Hz, 1H), 5.96 (d, *J* = 4.9 Hz, 1H), 4.70 (s, 3H), 3.87−3.81 (m, 3H), 3.47 (s, 1H), 1.95−1.85 (m, 1H), 1.77−1.65 (m, 3H), 1.55−1.52 (m, 4H), 1.30 (s, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.5, 133.4, 133.3, 128.8, 128.1, 127.9, 127.2, 126.5, 125.7, 114.1, 103.8, 90.1, 89.9, 80.8, 74.4, 74.0, 70.7, 29.9, 29.7, 28.3, 26.8, 26.4, 26.1, 18.3, 18.2, −3.8, −4.6; HRMS (ESI) calcd for $C_{29}H_{42}NaO_6Si$ $[M + Na]^+$ *m*/*z* = 538.2672, found 538.2671.

(3a*R*,4a*S*,5*S*,8a*R*,8b*R*)-5,8a-Bis(benzyloxy)-2,2-dimethyl-4a-((naphthalen-2-ylmethoxy)methyl)octahydro[1,3]dioxolo[4,5-*b*]benzofuran (27). A 1.0 M solution of TBAF (5.5 mL, 5.5 mmol) in THF was added to a stirred solution of **26** (0.948 g, 1.84 mmol) in THF (40 mL). After 24 h, the reaction was diluted with dichloromethane and (40 mL) and water (100 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 3 cm; 2:3 EtOAc/hexanes) to give the corresponding alcohol (**45**) as a light yellow solid (0.700 g, 95%): R_f = 0.27 (2:3 EtOAc/hexanes); mp 101−102 °C; $[\alpha]^{20}_{D}$ +33 (*c* 0.16, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.80 (m, 3H), 7.73 (s, 1H), 7.51−7.46 (m, 2H), 7.41 (dd, *J* = 8.4 Hz, 1.5 Hz, 1H), 5.96 (d, *J* = 4.5 Hz, 1H), 4.70 (s, 2H), 4.62 (d, *J* = 4.5 Hz, 1H), 3.77−3.70 (m, 3H), 3.52 (s, 1H), 2.63 (d, *J* = 5.1 Hz, 1H), 2.16−2.06 (m, 1H), 1.84−1.65 (m, 3H), 1.62−1.44 (m, 5H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6, 133.34, 133.27, 128.7, 128.1, 127.9, 126.5, 125.6, 114.0, 104.2, 90.5, 89.9, 80.5, 74.3, 73.9, 70.0, 31.3, 28.0, 26.3, 26.1, 16.9; HRMS (ESI) calcd for $C_{23}H_{28}NaO_6$ $[M + Na]^+$ *m*/*z* = 423.1778, found 423.1770. Sodium hydride (60% dispersion in mineral oil, 0.251 g, 6.25 mmol), benzyl bromide (0.775 g, 4.53 mmol), and tetrabutylammonium iodide (0.602 g, 1.63 mmol) were added sequentially to a stirred 0 °C solution of the preceding alcohol (**45**, 0.652 g, 1.63 mmol) in 1:1 DMF/THF (40 mL). The cooling bath was removed, and the reaction was allowed to warm to room temperature. After 3 h, methanol (10 mL) was added, and the resulting solution was diluted further with dichloromethane (40 mL) and water (40 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (2 × 40 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 3 cm; 1:9 EtOAc/hexanes) to give **27** as a colorless oil (0.861 g, 91%): R_f = 0.70 (1:1 EtOAc/hexanes); $[\alpha]^{20}_{D}$ +120 (*c* 0.350, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.79 (m, 1H), 7.72−7.70 (m, 2H), 7.70 (s, 1H), 7.48−7.43 (m, 2H), 7.40 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.32−7.17 (m, 10H), 6.14 (d, *J* = 5.4 Hz, 1H), 5.17 (d, *J* = 5.4 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 7.8 Hz, 1H), 4.61 (d, *J* = 7.8 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.02 (d, *J* = 9.9 Hz, 1H), 3.75 (d, *J* = 9.9 Hz, 1H), 3.35 (dd, *J* = 11.3, 5.0 Hz, 1H), 2.10−2.02 (m, 1H), 1.97−1.89 (m, 1H), 1.78−1.63 (m, 3H), 1.56 (s, 3H), 1.42−1.33 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.6, 136.2, 133.5, 133.1, 128.4, 128.2, 128.1, 127.9, 127.7, 127.5, 127.2, 126.3, 126.2, 126.0, 125.7, 114.0, 105.1, 91.7, 85.5, 85.4, 74.1, 73.2, 71.3, 66.8, 27.0, 26.1,

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25.8, 18.9; HRMS (ESI) calcd for $C_{37}H_{40}NaO_6$ $[M + Na]^+$ m/z = 603.2717, found 603.2714.

(2*R*,3*R*,3a*R*,7*S*,7a*S*)-3a,7-Bis(benzyloxy)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-7a-((naphthalen-2-ylmethoxy)methyl)octahydrobenzofuran-3-yl Acetate (28). $FeCl_3$·$6H_2O$ (0.419 g, 1.55 mmol) was added to a stirred 0 °C solution of **27** (0.901 g, 1.55 mmol) in dichloromethane (40 mL). The cooling bath was removed, and the reaction was allowed to warm to room temperature. After 1 h, a saturated solution of $NaHCO_3$ (50 mL) was added, and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 30 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3 cm; 35% EtOAc/hexanes) to afford the corresponding diol (**46**) as a colorless oil. Acetic anhydride (0.63 g, 6.2 mmol) was added to a stirred 0 °C solution of the preceding diol (**46**), pyridine (0.024 g, 0.31 mmol), and DMAP (19 mg, 0.15 mmol) in dichloromethane (30 mL). The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After 1 h, 1.0 M HCl (8 mL) and water (60 mL) were added. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 2.5 cm; 1:4 EtOAc/hexanes) to give the corresponding diacetate (**47**) as a colorless oil (0.698 g, 72% over 2 steps): R_f = 0.27 (1:4 EtOAc/hexanes); $[\alpha]^{20}_D$ +25 (*c* 0.075, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.77 (m, 4H), 7.52−7.45 (m, 3H), 7.32−7.20 (m, 10H), 6.79 (d, *J* = 6.0 Hz, 1H), 6.29 (d, *J* = 6.0 Hz, 1H), 4.85 (d, *J* = 12.6 Hz, 1H), 4.72 (d, *J* = 12.6 Hz, 1H), 4.67 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.1 Hz, 1H), 4.49 (d, *J* = 11.1 Hz, 1H), 4.42 (d, *J* = 11.9 Hz, 1H), 3.99 (d, *J* = 9.8 Hz, 1H), 3.79 (d, *J* = 9.8 Hz, 1H), 3.37 (dd, *J* = 10.8, 4.4 Hz, 1H), 2.34−2.26 (m, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 2.02−1.92 (m, 2H), 1.78−1.68 (m, 2H), 1.53−1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.0, 138.5, 138.2, 135.8, 133.5, 133.0, 128.4, 128.3, 128.2, 128.0, 127.7, 127.63, 127.57, 127.4, 126.04 126.01, 125.7, 125.5, 93.3, 86.3, 85.5, 76.9, 76.6, 73.8, 71.7, 66.1, 25.5, 24.7, 21.1, 20.7, 18.7; HRMS (ESI) calcd for $C_{38}H_{40}NaO_8$ $[M + Na]^+$ m/z = 647.2615, found 647.2610. A stirred mixture of thymine (0.311 g, 2.52 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (5.02 g, 24.7 mmol) in 1,2-dichloroethane (30 mL) was heated at 90 °C for 1 h until a clear colorless solution persisted. The resulting solution was cooled to 0 °C, and a solution of the preceding diacetate (**47**, 0.687 g, 0.995 mmol) in 1,2-dichloroethane (15 mL) and TMSOTf (0.550 g, 2.49 mmol mmol) were added sequentially. The cooling bath was removed, and the reaction mixture was heated at 55 °C. After 13 h, the reaction mixture was cooled to room temperature and poured into a saturated solution of $NaHCO_3$ (40 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 3 cm; 1:1 EtOAc/hexanes) to give nucleoside **28** as a white solid (0.615 g, 81%): R_f = 0.15 (2:3 EtOAc/hexanes); mp 71−74 °C; $[\alpha]^{20}_D$ +28 (*c* 0.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.87−7.75 (m, 5H), 7.51−7.42 (m, 3H), 7.37−7.17 (m, 10H), 6.39 (d, *J* = 5.9 Hz, 1H), 6.13 (d, *J* = 5.9 Hz, 1H), 4.78 (d, *J* = 12.2 Hz, 1H), 4.70−4.61 (m, 2H), 4.58−4.52 (m, 2H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.04 (d, *J* = 10.6 Hz, 1H), 3.77 (d, *J* = 10.6 Hz, 1H), 3.70−3.64 (m, 1H), 2.21−2.12 (m, 1H), 2.06 (s, 3H), 2.05−1.95 (m, 1H), 1.91−1.72 (m, 3H), 1.51−1.40 (m, 1H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 163.9, 151.2, 138.1, 137.8, 136.8, 135.0, 133.5, 130.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.93, 127.90, 127.8, 127.6, 126.4, 126.3, 126.1, 125.4, 111.0, 88.4, 86.7, 83.2, 78.8, 77.3, 73.8, 72.5, 72.2, 65.5, 26.8, 25.5, 20.9, 17.9, 11.9; HRMS (ESI) calcd for $C_{41}H_{42}N_2NaO_8$ $[M + Na]^+$ m/z = 713.2833, found 713.2847.

(2*R*,3*R*,3a*R*,7*S*,7a*S*)-3a,7-Bis(benzyloxy)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-7a-((naphthalen-2-ylmethoxy)methyl)octahydrobenzofuran-3-yl methanesulfonate (29). Potassium carbonate (0.141 g, 1.02 mmol) was added to a stirred solution of nucleoside **28** (0.561 g, 0.812 mmol) in methanol (25 mL). After 18 h, a solution of saturated NH_4Cl (25 mL), water (35 mL), and dichloromethane (80 mL) were added. The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 40 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford the corresponding alcohol (**48**) as a colorless solid (0.542 g, 93%), which was used in the next step without further purification: R_f = 0.26 (2:3 EtOAc/hexanes); mp 79−83 °C; $[\alpha]^{20}_D$ +26 (*c* 0.060, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.83−7.79 (m, 1H), 7.78−7.73 (m, 2H), 7.66 (s, 1H), 7.49−7.44 (m, 4H), 7.40−7.29 (m, 7H), 7.25−7.18 (m, 3H), 7.14−7.10 (m, 2H), 6.07 (d, *J* = 2.0 Hz, 1H), 4.77−4.67 (m, 4H), 4.60 (d, *J* = 12.1 Hz, H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.42−4.36 (m, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.17 (br d, *J* = 3.8 Hz, 1H), 3.94 (d, *J* = 11.4 Hz, 1H), 3.86 (d, *J* = 11.4 Hz, 1H), 2.32−2.22 (m, 1H), 1.84−1.75 (m, 4H), 1.60−1.51 (m, 2H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 151.0, 137.8, 137.0, 136.8, 135.2, 133.3, 133.2, 128.9, 128.6, 128.5, 128.4, 128.0, 127.9, 127.6, 126.8, 126.5, 126.3, 125.8, 93.8, 90.7, 84.9, 81.1, 73.9, 73.2, 71.0, 64.5, 29.9, 27.4, 25.7, 18.1, 12.2; HRMS (ESI) calcd for $C_{39}H_{40}N_2NaO_7$ $[M + Na]^+$ m/z = 671.2728, found 671.2738. Methanesulfonyl chloride (0.287 g, 2.51 mmol) was added to a stirred 0 °C solution of the preceding alcohol (**48**, 0.542 g, 0.835 mmol) and DMAP (0.010 g, 0.082 mmol) in anhydrous pyridine (25 mL). The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After 16 h, a saturated solution of $NaHCO_3$ (40 mL) and dichloromethane (40 mL) were added. The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with 1.0 M HCl (2 × 40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 2.5 cm; 1:1 EtOAc/hexanes) to give nucleoside **29** as a colorless solid (0.569 g, 94%): R_f = 0.33 (1:1 EtOAc/hexanes); mp 83−86 °C; $[\alpha]^{20}_D$ +48 (*c* 0.070, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.82−7.75 (m, 4H), 7.55 (s, 1H), 7.49−7.45 (m, 2H), 7.42−7.40 (m, 1H), 7.39−7.35 (m, 2H), 7.34−7.29 (m, 2H), 7.28−7.25 (m, 1H), 7.23−7.15 (m, 5H), 6.45 (d, *J* = 4.5 Hz, 1H), 5.53 (d, *J* = 4.4 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.72−4.61 (m, 3H), 4.58−4.53 (m, 2H), 4.00−3.96 (m, 2H), 3.85 (d, *J* = 11.0 Hz, 1H), 2.84 (s, 3H), 2.23−2.13 (m, 1H), 2.06−1.91 (m, 2H), 1.89−1.80 (m, 1H), 1.68−1.59 (m, 1H), 1.55−1.46 (m, 1H), 1.23 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 151.0, 138.2, 137.4, 136.2, 135.0, 133.5, 133.2, 128.7, 128.62, 128.58, 128.56, 128.12, 128.08, 128.0, 127.9, 127.8, 126.7, 126.5, 126.3, 125.7, 111.7, 89.4, 87.6, 85.2, 83.6, 77.2, 73.9, 72.3, 71.6, 65.1, 39.1, 27.4, 25.3, 17.5, 12.0; HRMS (ESI) calcd for $C_{40}H_{42}N_2NaO_9S$ $[M + Na]^+$ m/z = 749.2503, found 749.2521.

((5a*R*,6a*S*,7*S*,10a*R*,10b*S*)-7,10a-Bis(benzyloxy)-3-methyl-2-oxo-7,8,9,10,10a,10b-hexahydro-2*H*-benzofuro[2′,3′:4,5]-oxazolo[3,2-*a*]pyrimidin-6a(5a*H*)-yl)methyl Methanesulfonate (30). DBU (0.435 mL, 3.13 mmol) was added to a stirred solution of **29** (0.569 g, 0.783 mmol) in acetonitrile (45 mL). The reaction mixture was heated at 80 °C for 75 h, cooled to 0 °C, and diluted with dichloromethane (45 mL). The resulting solution was poured into a solution of 0.6 M HCl (40 mL), and the layers were separated. The aqueous phase was extracted with dichloromethane (2 × 25 mL), and the combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 2.5 cm; 3% EtOH/EtOAc) to give the corresponding 2,2′-anhydronucleoside (**49**) as a colorless solid (0.347 g, 71%): R_f = 0.35 (7% EtOH/EtOAc); mp 79−83 °C; $[\alpha]^{20}_D$ −21 (*c* 0.061, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.76 (m, 3H), 7.67 (s, 1H), 7.52−7.43 (m, 2H), 7.37−7.25 (m, 6H), 7.20−7.13 (m, 4H), 7.12−7.05 (m, 2H), 5.93 (d, *J* = 6.2 Hz, 1H), 5.33 (d, *J* = 6.2 Hz, 1H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.59−4.53 (m, 3H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.15 (d, *J* = 3.0 Hz, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 3.64 (d, *J* = 11.0 Hz, 1H), 2.35−2.26 (m, 1H), 1.93−1.84 (m, 4H), 1.77−1.65 (m, 2H), 1.64−1.55 (m, 1H), 1.40−1.30 (m, 1H); ^{13}C NMR (100 MHz,

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$CDCl_3$) δ 172.5, 159.8, 138.6, 138.0, 135.2, 130.5, 128.8, 128.5, 128.2, 128.1, 127.9, 127.8, 127.63, 127.59, 127.0, 126.4, 126.0, 118.8, 91.0, 89.5, 85.0, 83.6, 74.1, 72.6, 70.4, 67.1, 29.9, 28.1, 25.5, 16.2, 14.3; HRMS (ESI) calcd for $C_{39}H_{38}N_2NaO_6$ $[M + Na]^+$ m/z = 653.2622, found 653.2627. DDQ (0.315 g, 1.39 mmol) was added to a stirred solution of the preceding 2,2′-anhydronucleoside (**49**, 0.286 g, 0.461 mmol) in 1:9 water/dichloromethane (28 mL). After 3 h, the reaction mixture was poured into a solution of saturated $NaHCO_3$ (50 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2 cm; 7% EtOH/EtOAc) to give the corresponding alcohol as a colorless solid (**50**, 0.220 g, 96%): R_f = 0.43 (7% EtOH/EtOAc); mp 105−107 °C; $[\alpha]^{20}_D$ −14 (*c* 0.060, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.10 (m, 11H), 5.65 (d, *J* = 5.7 Hz, 1H), 5.08 (d, *J* = 5.7 Hz, 1H), 4.39−4.53 (m, 4H), 3.94−3.88 (m, 1H), 3.75−3.64 (m, 1H), 3.62−3.55 (m, 1H), 2.68−2.64 (m, 1H), 2.04−1.95 (m, 1H), 1.78−1.68 (m, 4H), 1.65−1.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 160.0, 137.8, 137.1, 128.6, 128.5, 128.0, 127.8, 118.5, 89.3, 88.2, 85.9, 84.3, 77.0, 72.7, 67.4, 63.1, 29.7, 28.6, 25.4, 17.7, 14.0; HRMS (ESI) calcd for $C_{28}H_{30}N_2NaO_6$ $[M + Na]^+$ m/z = 513.1996, found: 513.1997. Methanesulfonyl chloride (0.130 g, 1.14 mmol) was added to a stirred 0 °C solution of the preceding alcohol (**50**, 0.221 g, 0.451 mmol) and DMAP (5.5 mg, 0.045 mmol) in anhydrous pyridine (20 mL). The cooling bath was removed, and the reaction was allowed warm to room temperature. After 12 h, the reaction mixture was diluted with dichloromethane (50 mL) and poured into a saturated solution of $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic extracts were washed with 1.0 M HCl (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (17 × 2 cm; 7% EtOH/EtOAc) to give 2,2′-anhydronucleoside **30** as a colorless solid (0.226 g, 93%): R_f = 0.28 (10% EtOH/EtOAc); mp = 99−101 °C; $[\alpha]^{20}_D$ +30 (*c* 0.064, $CHCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.16 (m, 11H), 6.05 (d, *J* = 5.9 Hz, 1H), 5.30 (d, *J* = 6.0 Hz, 1H), 4.68−4.54 (m, 3H), 4.51−4.42 (m, 2H), 4.26 (d, *J* = 11.1 Hz, 1H), 3.94 (d, *J* = 4.0 Hz, 1H), 2.76 (s, 3H), 2.23−2.06 (m, 1H), 1.92−1.89 (m, 5H), 1.75−1.48 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 159.6, 137.5, 137.4, 130.5, 128.6, 128.1, 128.0, 127.9, 127.8, 118.7, 89.6, 88.3, 84.4, 84.2, 75.9, 72.6, 69.1, 67.3, 37.0, 30.0, 27.9, 25.1, 16.3, 14.1; HRMS (ESI) calcd for $C_{29}H_{32}N_2NaO_8S$ $[M + Na]^+$ m/z = 591.1772, found 591.1768.

1-((2*R*,3*S*,3a*R*,7*S*,7a*S*)-3a,7-Bis(benzyloxy)hexahydro-2*H*-3,7a-(epoxymethano)benzofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (31). A 2.0 M solution of NaOH (0.42 mL, 0.84 mmol) was added to stirred suspension of 2,2′-anydronucleoside **30** (0.220 g, 0.387 mmol) in 1:1 water/ethanol (50 mL). The reaction was heated at 100 °C for 30 min, cooled to room temperature, and diluted with dichloromethane (50 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 2 cm 3:2 EtOAc/hexanes) to give tricyclic nucleoside **31** as a colorless solid (0.181 g, 96%): R_f = 0.92 (5% EtOH/EtOAc); mp 96−99 °C; $[\alpha]^{20}_D$ +121 (*c* 0.100, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.58 (s, 1H), 7.48−7.24 (m, 10H), 6.05 (s, 1H), 4.78−4.66 (m, 2H), 4.57−4.46 (m, 3H), 4.21 (d, *J* = 8.0 Hz, 1H), 4.16 (d, *J* = 8.1 Hz, 1H), 3.81−3.74 (m, 1H), 2.18 (br d, *J* = 11.6 Hz, 1H), 2.08−2.02 (m, 1H), 1.98 (s, 3H), 1.90−1.84 (m, 1H), 1.82−1.64 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 150.8, 138.2, 137.8, 135.8, 128.6, 128.5, 128.0, 127.9, 127.72, 127.68, 109.7, 89.7, 89.1, 86.3, 77.3, 74.8, 74.4, 71.5, 67.5, 26.1, 23.3, 20.4, 12.8; HRMS (ESI) calcd for $C_{28}H_{30}N_2NaO_6$ $[M + Na]^+$ m/z = 513.1996, found 513.1993.

1-((2*R*,3*S*,3a*R*,7*S*,7a*S*)-3a,7-Dihydroxyhexahydro-2*H*-3,7a-(epoxymethano)benzofuran-2-yl)-5-methylpyrimidine-2,4-(1*H*,3*H*)-dione (32). Pearlman's catalyst (0.026 g, 0.038 mmol) was added to a stirred solution of tricyclic nucleoside **31** (0.184 g, 0.375 mmol) in a 1:1 mixture of EtOH/MeOH (30 mL), which was placed under an atmosphere of hydrogen gas via a hydrogen-filled balloon. After 15 h, the reaction mixture was filtered through sintered glass funnel, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (15 × 2 cm; 5% EtOH/EtOAc) to give tricyclic nucleoside **32** as a colorless solid (0.114 g, 98%): R_f = 0.22 (5% EtOH/EtOAc); mp 209−210 °C; $[\alpha]^{20}_D$ +158 (*c* 0.060, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD) δ 7.98 (d, *J* = 1.0 Hz, 1H), 5.91 (d, *J* = 1.0 Hz, 1H), 4.28 (d, *J* = 1.1 Hz, 1H), 4.09 (s, 2H), 3.89 (dd, *J* = 10.7, 4.8 Hz, 1H), 1.92 (d, *J* = 1.1 Hz, 3H), 1.87−1.73 (m, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.7, 152.2, 138.2, 109.9, 90.7, 90.0, 82.0, 81.8, 74.8, 68.3, 30.6, 28.6, 21.5, 12.4; HRMS (ESI) calcd for $C_{14}H_{18}N_2NaO_6$ $[M + Na]^+$ m/z = 333.1057, found 333.1061.

(2*R*,3*S*,3a*R*,7*S*,7a*S*)-3a-Hydroxy-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)hexahydro-2*H*-3,7a-(epoxymethano)benzofuran-7-yl 4-Oxopentanoate (6: R_1 = Lev, R_2 = H, Bx = thymine). Mukaiyama's reagent (0.075 g, 0.29 mmol) was added to a stirred solution of tricyclic nucleoside **32** (0.070 g, 0.23 mmol) and levulinic acid (28 μL, 0.27 mmol) in acetonitrile (11 mL). After 15 min, triethylamine (94 μL, 0.68 mmol) and DMAP (0.008 g, 0.07 mmol) were added. After an additional 16 h, the reaction mixture was poured into an ice-cold solution of 1 M HCl (20 mL) and further diluted with dichloromethane (15 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL), dried through a phase separator cartridge, and concentrated under reduced pressure. The residue was purified by flash column chromatography (15 × 1.5 cm; 1:20 MeOH/CH_2Cl_2) to afford tricyclic nucleoside **6** (R_1 = Lev, R_2 = H, Bx = thymine) as a colorless solid (0.070 g, 76% yield): R_f = 0.24 (1:15 MeOH/CH_2Cl_2); mp 238−239 °C (CH_2Cl_2); $[\alpha]_D^{20}$ +34 (*c* = 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.32 (s, 1H), 7.80 (s, 1H), 5.99 (s, 1H), 5.33 (s, 1H), 5.12−4.99 (m, 1H), 4.29 (s, 1H), 4.03 (d, *J* = 9.8 Hz, 1H), 3.99 (d, *J* = 9.7 Hz), 2.86 (ddd, *J* = 18.7, 9.1, 4.4 Hz, 1H), 2.75 (ddd, *J* = 18.6, 6.4, 4.1 Hz, 1H), 2.57 (ddd, *J* = 16.9, 9.1, 4.1 Hz, 1H), 2.45 (ddd, *J* = 17.0, 6.6, 4.4 Hz, 1H), 2.16 (s, 3H), 1.98 (s, 3H), 1.96−1.78 (m, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 207.7, 172.9, 164.1, 150.7, 136.6, 110.1, 89.3, 88.3, 82.4, 80.2, 74.3, 70.0, 38.8, 29.9, 28.7, 27.9, 26.6, 20.9, 12.5; HRMS (ESI) calcd for $C_{19}H_{25}N_2O_8$ $[M + H]^+$ m/z = 409.1605, found 409.1596.

(2*R*,3*S*,3a*R*,7*S*,7a*S*)-3a-(((2-Cyanoethoxy)(diisopropylamino)-phosphanyl)oxy)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)hexahydro-2*H*-3,7a-(epoxymethano)benzofuran-7-yl 4-Oxopentanoate (33). 2-Cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite (90 μL, 0.39 mmol) was added to a stirred solution of nucleoside **6** (R_1 = Lev, R_2 = H, Bx = thymine) (0.064 g, 0.16 mmol), *N*,*N*-diisopropylethylamine (70 μL, 0.39 mmol), and *N*-methylimidazole (1 drop) in dichloromethane (1.5 mL). After 2 h, additional portions of *N*,*N*-diisopropylethylamine (35 μL) and 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite (30 μL) were added, and the stirring was continued for another 10 min. The reaction was then cooled in an ice bath and quenched by the addition of diisopropylethylamine (0.1 mL) and methanol (0.8 mL). After another 10 min of stirring in the ice bath, the solvents were evaporated under reduced pressure, and the residue was purified by column chromatography (20% to 30% acetone/dichloromethane) to give phosphoramidite **33** (57 mg, 60%): R_f = 0.34 (1:4 acetone/dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02 (br s, 1H), 7.85 (d, *J* = 5.0 Hz, 1H), 6.09 (br s, 1H), 5.07 (br s, 1H), 4.71 (d, *J* = 3.8 Hz, 1H), 4.29−3.99 (m, 4H), 3.84 (d, *J* = 11.5 Hz, 2H), 3.70−3.40 (m, 5H), 2.97−2.55 (m, 9H), 2.49 (br s, 1H), 2.33−2.13 (m, 4H), 2.09−1.94 (m, 5H), 1.86 (br s, 5H), 1.41−1.01 (m, 33H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 145.8, 144.8; LRMS (ESI) calcd for $C_{28}H_{41}N_4O_9P$ $[M + H]^+$ m/z = 608.3, found 608.3.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds, as well as X-ray crystallography reports and CIF files for compounds **19** and **32**.

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Notes

The authors declare no competing financial interest.

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