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# Synthesis of *cis*- and *trans*-α-L-[4.3.0]Bicyclo-DNA Monomers for Antisense Technology: Methods for the Diastereoselective Formation of Bicyclic Nucleosides

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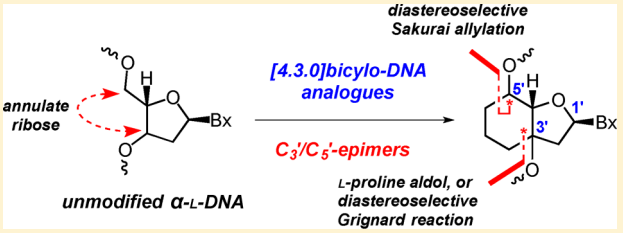
Supporting Information

**ABSTRACT:** Two α-L-*ribo*-configured bicyclic nucleic acid modifications, represented by analogues **12** and **13**, which are epimeric at $C_3'$ and $C_5'$ have been synthesized using a carbohydrate-based approach to build the bicyclic core structure. An intramolecular L-proline-mediated aldol reaction was employed to generate the *cis*-configured ring junction of analogue **12** and represents a rare application of this venerable organocatalytic reaction to a carbohydrate system. In the case of analogue **13**, where a *trans*-ring junction was desired, an intermolecular diastereoselective Grignard reaction followed by ring-closing metathesis was used. In order to set the desired stereochemistry at the $C_5'$ positions of both nucleoside targets, a study of diastereoselective Lewis acid mediated allylation reactions on a common bicyclic aldehyde precursor was carried out. Analogue **12** was incorporated in oligonucleotide sequences, and thermal denaturation experiments indicate that it is destabilizing when paired with complementary DNA and RNA. However, this construct shows a significant improvement in nuclease stability relative to a DNA oligonucleotide.




## INTRODUCTION

Conformational restriction of the ribose or deoxyribose sugar moieties of nucleoside monomers has been an area of intense research interest in recent years.[1] Chemically modified oligonucleotides which incorporate these monomers are being investigated as small-interfering RNAs (siRNAs) and as antisense agents for post-translational control of gene expression.[2] Structural modifications that restrict the conformation of the furanose ring in the $C_3'$-*endo* (N-type or northern) or $C_2'$-*endo* (S-type or southern) sugar puckers while maintaining Watson−Crick base-pairing properties are particularly well-suited for the antisense approach. These analogues improve binding affinity of the modified oligonucleotides (ONs) for DNA and RNA complements, as measured by increased duplex stability in thermal denaturation experiments ($T_m$). One of the most successful examples of such structural modifications has come from independent reports by Imanishi[3] and Wengel,[4] who have described the synthesis and base-pairing properties of 2′,4′-bridged nucleic acids (BNA), commonly known as locked nucleic acids (LNAs, i.e., **1** and **2**; Figure 1). The 1,4-dioxabicyclo[2.2.1]heptane core of these nucleoside monomers locks the ribose sugar moiety in the N-type conformation, and oligonucleotides that incorporate this modification show significant increases in duplex thermostability ($\Delta T_m$ = +4−10 °C/mod vs RNA), which makes them useful for diagnostic and antisense applications.[5]

Other research groups have investigated the effects of linearly annulating the furanose rings of designed nucleoside systems, which also provides conformational restriction of the sugar pucker (Figure 1). Leumann and co-workers appended a five-membered carbocyclic ring to the furanose system of DNA to give bicyclo-DNA (bc-DNA) **3**.[6−8] Even though this strategy of conformational constraint resulted in simultaneous restriction of the torsion angles γ and δ in bc-DNA, it did not improve thermal stability relative to DNA ($\Delta T_m$ = 0 to +0.5 °C/mod vs RNA). The lack of improvement in binding affinity was attributed to restriction of the torsion angle γ in the *ap* range, a consequence of the pseudoequatorial orientation of the 5′-OH group, as opposed to the +*sc* range seen in normal DNA. To rectify this, Leumann designed tricyclo-DNA (tc-DNA) **4** ($\Delta T_m$ = +2−4 °C/mod vs RNA) by appending a cyclopropane ring onto the annulated cyclopentane ring of bc-DNA.[9,10] However, subsequent structural studies showed that improvement in duplex thermal stability with tc-DNA results from a compensatory change in the torsion angles β and γ.[11] Interestingly, Imanishi showed that the torsion angle γ can be restricted in the +*sc* range in a [3.3.0] bicyclic ring system using the $N_5'$-phosphoramidate-linked 5′-amino-3′,5′-bridged nucleic acid analogue **5**.[12] This modification was found to be stabilizing ($\Delta T_m$ = +2 °C/mod vs RNA) relative to DNA, bc-DNA, and

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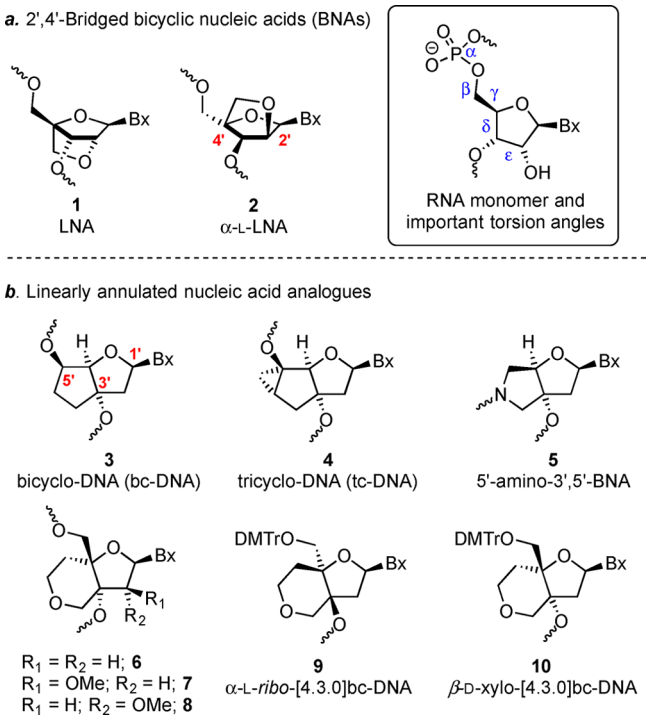


**Figure 1.** Structurally modified nucleic acid analogues.

5′-amino DNA. Imanishi has also described the synthesis and hybridization properties of [4.3.0] bicyclic nucleic acid analogues **6**–**8**. The furanose ring in all of these modifications is locked in the S-type conformation, however, these analogues proved to be moderately to extremely destabilizing relative to DNA ($\Delta T_m$ = −3 to −10 °C/mod vs RNA).[13,14] Nielsen and co-workers have reported the synthesis of the *α*-L-*ribo*-configured version (**9**) of the [4.3.0] bicyclic nucleoside **6**.[15] Unfortunately, they were unable to convert the 5′O-DMTr-protected nucleoside to the corresponding phosphoramidite for incorporation into oligonucleotide sequences. However, they evaluated the $C_3'/C_4'$ epimer (**10**) of analogue **9** in $T_m$ studies and found it to be extremely destabilizing relative to DNA ($\Delta T_m$ = −10 °C/mod vs RNA).

In an attempt to further refine the hybridization properties of bc-DNA (**3**), Leumann and co-workers synthesized a homologated analogue of the nucleic acid that contains a bicyclo[4.3.0]nonane core structure as in **11** (Figure 2).[16] The cyclohexane ring system in **11** is expected to orient the 5′-OH group in either an axial (desired) or equatorial (undesired) orientation. Molecular modeling experiments indicated that the undesired conformation **B** (torsion angle *γ* in the *ap* range) was 3.2 kcal/mol lower in energy in comparison to conformation **A** (torsion angle *γ* in the +*sc* range) in nucleoside monomer **11**. Evaluation of oligonucleotides containing **11** in thermal denaturation experiments indicated that this modification was slightly destabilizing relative to DNA ($\Delta T_m$ = −0.7 to −2.3 °C/mod vs RNA), except when introduced in tandem, where it was found to be slightly stabilizing ($\Delta T_m$ = +0.7 °C/mod vs RNA).

As part of our own efforts in de novo design of nucleic acid mimics for antisense applications, we wanted to evaluate the properties of nucleoside modification **12**, which is essentially the *α*-L-configured version of nucleoside **11**. Wengel and co-workers[17,18] previously evaluated all eight stereoisomers of LNA (**1**) and showed that *α*-L-LNA (**2**, i.e., the $C_1'$ epimer of *ent*-LNA) possesses similar hybridization properties in comparison to **1** ($\Delta T_m$ = +5–+10 °C/mod vs RNA). Given the interesting structural and biophysical properties of *α*-L-LNA-modified oligonucleotides, a number of related analogues were synthesized and investigated as potential agents for use in oligonucleotide-based diagnostic and therapeutic antisense applications.[19] Our own investigation of this interesting nucleic acid scaffold has recently led to synthetic, biophysical, and biological studies of several *α*-L-LNA analogues.[20] In addition, we have also described the duplex stabilizing properties of a tricyclic *α*-L-LNA analogue, which provides unprecedented increases in duplex thermal stability by simultaneously locking the sugar pucker (N-type conformation) and restricting rotation around the torsion angle *γ*.[21] In line with this work, we proposed to study the *α*-L-configured DNA analogue **12** and its $C_3'/C_5'$ epimer **13**, which lack the 2′,4′-oxamethylene bridge of *α*-L-LNA but have restricted rotation around the torsion angle *γ*. Conformational analysis of the cyclohexane ring in **12** suggested that the six-membered ring can exist in two chair conformations (Figure 2). Conformer **A** is capable of orienting the nucleobase, 5′-OH, and 3′-OH groups in precisely the same orientation as that observed for *α*-L-LNA monomers in an NMR-derived structure of a modified duplex with RNA (see overlay structure, Figure 2),[22] while conformer **B** would orient these vectors in distinctly different trajectories. In contrast, the cyclohexane ring in **13** was expected to exist in a single chair conformation (5′-OH equatorial and 3′-OH axial) by virtue of

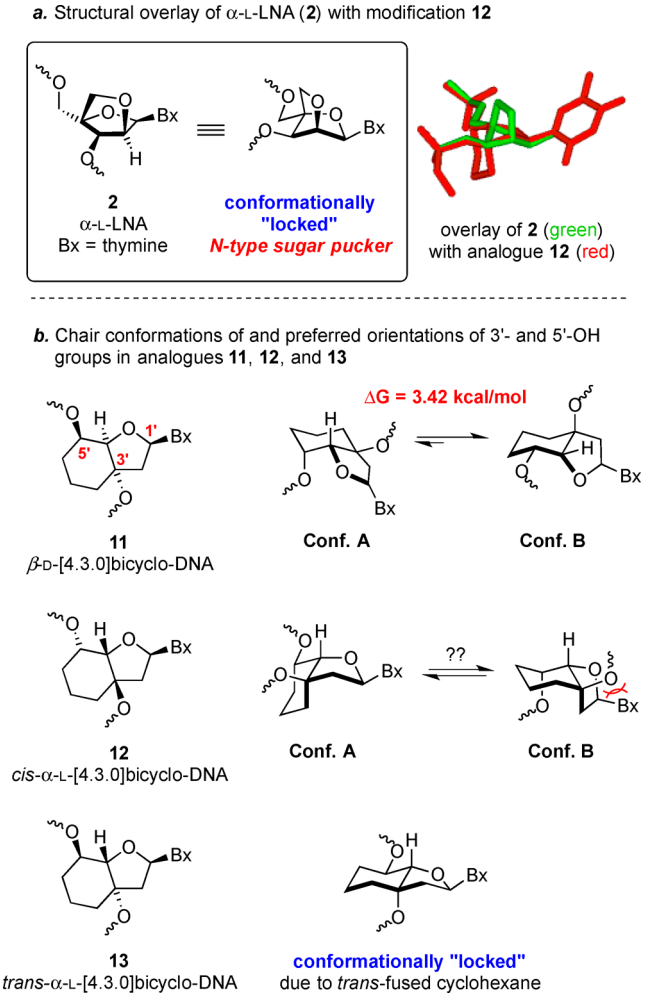


**Figure 2.** Rational design of bicyclo-DNA (bc-DNA) analogue **12**.


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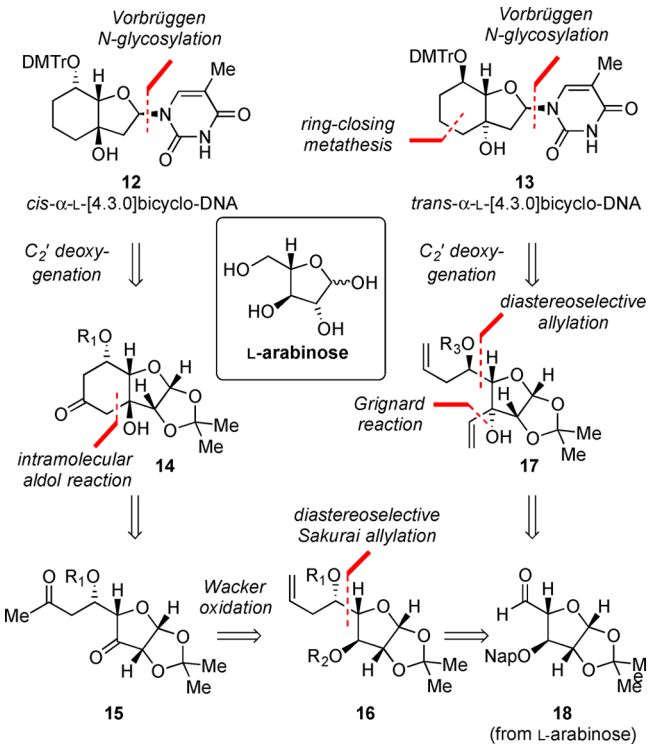
the increased rigidity of the *trans*-fused ring system. However, it was not clear if conformer **A** or **B** would be preferred when **12** was incorporated into oligonucleotide sequences, and paired, versus complementary nucleic acids, or if modifications such as **13** could be useful to stabilize oligonucleotide duplexes. To investigate these issues, we undertook the synthesis of **12** and **13** and studied the biophysical properties of the modified oligonucleotides.

## RESULTS AND DISCUSSION

It was envisaged that both α-L-[4.3.0]bicyclo-DNA analogues **12** and **13** could originate from L-arabinose as a common chiron (Scheme 1). In the case of *cis*-α-L-[4.3.0]bicyclo-DNA

**Scheme 1. Retrosynthetic Analysis of [4.3.0]Bicyclo-DNA Monomers 12 and 13**




(**12**), a key reaction would involve an intramolecular L-proline-catalyzed aldol reaction[23] of diketone **15**. The (*S*)-configured homoallylic alcohol present in **16** could be installed via a diastereoselective Sakurai allylation reaction of **18.** The synthetic blueprint of *trans*-α-L-[4.3.0]bicyclo-DNA (**13**) relied on the construction of the carbocyclic ring of the nucleoside monomer via a ring-closing metathesis reaction from diene **17**, also obtained via a diastereoselective allylation reaction. The tertiary alcohol at $C_3$ would originate from a stereoselective Grignard vinylation of a ketone.

To this end, L-arabinose was converted to isopropylidene derivative **19** using a known two-step procedure (Scheme 2).[24] Protection of the remaining free hydroxyl group as the *O*-Nap ether (Nap = 2-naphthylmethyl), followed by cleavage of the TBDPS group, furnished primary alcohol **20** (Scheme 2). Oxidation of **20** under Parikh–Doering reaction conditions gave the desired aldehyde precursor **18** in 94% yield. With this key synthetic intermediate in hand, attention was turned to finding optimal allylation reaction conditions that would give the desired *S*- and *R*-configured homoallylic alcohols, for the synthesis of **12** and **13**, respectively, with high diastereoslectivity. Following a protocol that had been developed by Danishefsky and co-workers,[25] treatment of **18** with allyltrimethylsilane in the presence of boron trifluoride diethyl etherate furnished **21** as a single diastereomer. However, obtaining the epimeric and (*R*)-configured homoallyic alcohol intermediate to be used in the synthesis of **17** proved to be more challenging (Table 1). Variation of the Lewis acid and nucleophile source were systematically explored, and it was discovered that the combination of 3.0 equiv of magnesium bromide diethyl etherate and 2.0 equiv of allyltributyltin at −78 °C in dichloromethane gave the best results (94%, dr = 4:1; Table 1, entry 8). It is possible that use of allyltributylstannane in combination with $MgBr{\cdot}OEt_2$ is operative under chelation control to give the $C_5$-*epi*-**21** isomer as the major product.

Benzylation of **21**, followed by selective cleavage of the Nap ether protecting group using DDQ,[26,33] gave **22** in 66% yield over two steps. Sequential oxidation reactions, first of the $C_3$ alcohol in **22** to **23** and then of the terminal olefin according to Smith and co-workers[27] gave diketone **24**. At this juncture, the opportunity presented itself to utilize the mild catalytic conditions of the Hajos–Parrish–Eder–Sauer–Weichert reaction[23] to circumvent any possible epimerization and to ensure isolation of the desired β-hydroxy ketone, which would later be the site (tertiary alcohol) of phosphoramidite formation to be used in oligonucleotide synthesis. It was also discovered that heating the reaction mixture in DMSO (or DMF) significantly shortened the reaction time while giving yields comparable to those obtained at room temperature.[28] The stereochemistry of the newly created stereogenic centers at $C_3$ and $C_5$ were assigned on the basis of an X-ray crystal structure obtained for the PMB ether **26**.[28]

Reduction of β-hydroxy ketone **25** using the Evans–Saksena[29] protocol gave alcohol **27**, which was directly converted to the thiocarbonyl imidazole derivative and then subjected to a Barton–McCombie[30] radical deoxygenation reaction in the presence of $Bu_3SnH$ in refluxing toluene to give **28** in 72% yield for the three-step sequence (Scheme 3). Cleavage of the isopropylidene group with DOWEX 50W8X acidic resin and acetylation gave a diastereomeric mixture of diacetates **29.** Application of the Vorbrüggen reaction conditions[31] furnished nucleoside **30** in 95% yield. After serving its role in securing the correct β-orientation of the thymine nucleobase via neighboring group participation, the $C_2'$-OAc group was cleaved and the $C_2'$ alcohol was converted to thiocarbamate **31** (52% over two steps) and then subjected to another radical deoxygenation reaction to give **32** in 80% yield. Hydrogenolysis of the benzyl ether, followed by alkylation of the resulting free alcohol as the 4,4′-dimethoxytrityl ether, completed the synthesis of *cis*-α-L-[4.3.0]bicyclo-DNA monomer **12**.

The synthesis of the second bicyclic nucleoside target **13** commenced with a diastereoselective allylation reaction of the common aldehyde intermediate **18**, which gave the desired (*R*)-configured homoallylic alcohol $C_5$-*epi*-**21** in excellent yield (93%, dr = 4:1, vide infra, Table 1, entry 8). A similar protecting group and oxidation sequence that had been developed for the synthesis of **12** was employed here to give ketone **34** (Scheme 4). Reaction with vinylmagnesium bromide in THF led to **35** as a single isomer. Unlike the synthetic route to **12** (Scheme 3), where the carbocyclic ring was formed before the thymine nucleobase was introduced, it was critical to reverse these synthetic operations in the synthesis of analogue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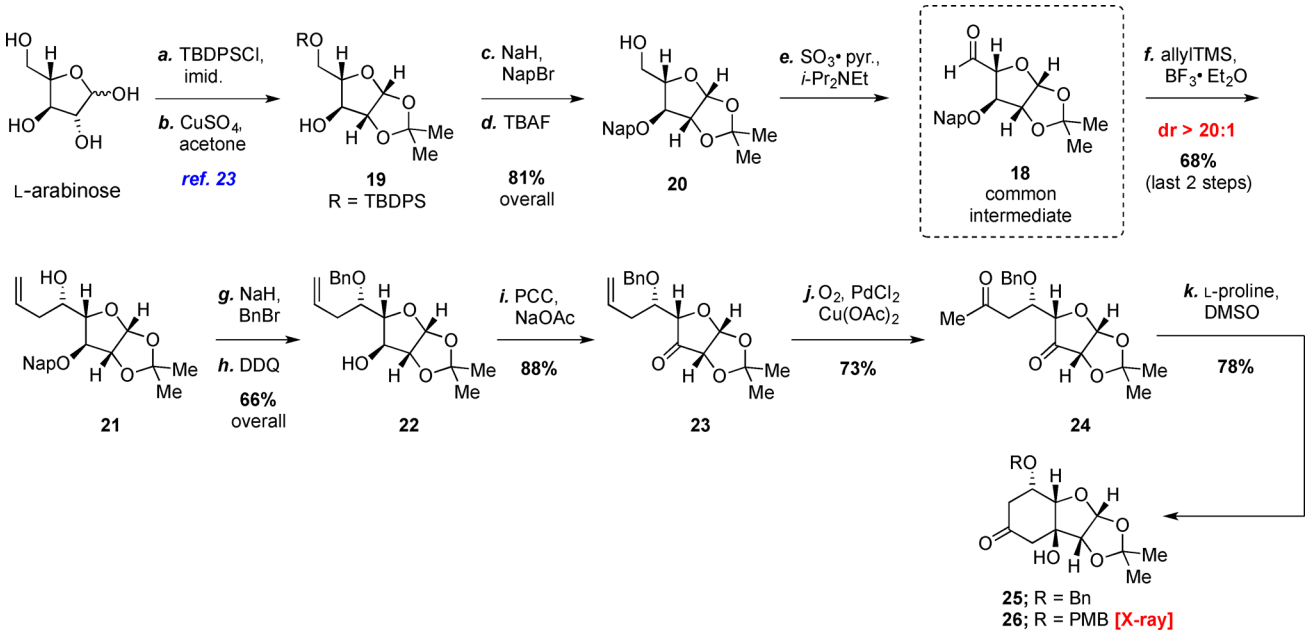
**Scheme 2. Synthesis of Tricyclic Ketone 25**[a]




[a]Conditions: (a) TBDPSCl, imidazole, DMF, 60 °C, 4 h; (b) $CuSO_4$, $H_2SO_4$, acetone, 23 °C, 1 h; (c) NapBr, NaH, TBAI, DMF/THF (1/1), 23 °C, 2 h; (d) TBAF, THF, 23 °C, 4 h; (e) $SO_3$·pyridine, *i*-$Pr_2NEt$, $CH_2Cl_2$/DMSO (5/1), −20 to 0 °C, 30 min; (f) allylTMS, $BF_3$·$Et_2O$, $CH_2Cl_2$, −78 °C, 2 h, dr > 20:1; (g) NaH, BnBr, TBAI, DMF/THF (1/1), 23 °C, 2 h; (h) DDQ, $CH_2Cl_2$/$H_2O$ (9/1), 23 °C, 6 h; (i) PCC, NaOAc, $CH_2Cl_2$, 23 °C, 6 h; (j) $O_2$, $PdCl_2$, $Cu(OAc)_2$, $H_2O$/DMA (1/7), 23 °C, 24 h; (k) L-proline, DMSO, 55 °C, 24 h.

**13**. Others have reported unwanted side reactions to occur when related *trans*-1-oxabicyclo[4.3.0]nonane systems have been subjected to acidic hydrolysis of a $C_1$,$C_2$-isopropylidene group,[32] and a similar result was observed with the $C_3$/$C_5$-epimer of **28**. Therefore, treatment of **35** with DOWEX 50W8X, acetylation of the resulting mixture of diastereomeric diols, and application of the Vorbrüggen reaction furnished **37** in 81% yield over three steps. Exposure of **37** to Grubbs' second-generation catalyst, followed by hydrogenation of the resulting cyclohexene ring and cleavage of the $C_2'$-OAc group, afforded bicyclic nucleoside **38**. Barton−McCombie deoxygenation gave **39**, which was converted to DMTr ether **13**. Unlike similar deoxygenation reactions on nucleoside systems, which have been reported to be low-yielding and problematic with respect to reproducibility,[16] all Barton−McCombie deoxygenation reactions that were used in the synthesis of **12** and **13** proved to be uneventful and straightforward.

Nucleoside analogues **12** and **13** were converted to the corresponding phosphoramidites **40** and **41**, respectively. However, only phosphoramidite **40** could be successfully incorporated into oligonucleotide sequences using a standard protocol.[34] Unfortunately, all attempts to incorporate phosphoramidite **41** (Scheme 5) into oligonucleotides using the conditions employed for the incorporation of **40** were unsuccessful. The inability to incorporate nucleosides with *trans*-fused bicyclic ring systems into oligonucleotides has been documented previously.[14,15]

Oligonucleotides were synthesized in over 90% yield at 2 μM scale on an automated DNA synthesizer using dT-controlled pore glass (CPG) polymer support for **A2** and **A3**, and dC−CPG support for **A5** as described previously.[34]

The duplex stabilizing properties of **12** were evaluated using single, double, and triple incorporations of the modified nucleotide into two oligonucleotide sequences (**A1** and **A4**, Table 2). In the first sequence (**A1**), we introduced **12** into a stretch of dT nucleotides as either single (**A2**) or tandem incorporations (**A3**) of the modified nucleotide. We also incorporated **12** between purine nucleotides using a second oligonucleotide sequence (**A4**) to provide a sequence context for the $T_m$ experiments. A single incorporation of **12** (**A2**) produced a −3.7 °C reduction in duplex thermal stability when paired with its complementary RNA strand, while two incorporations in tandem were also destabilizing (**A3**, $\Delta T_m$ −2.9 °C/mod). Three incorporations of the modified nucleotide **12** introduced at positions 5, 8, and 10 of oligonucleotide **A4** were slightly less destabilizing (**A5**, $\Delta T_m$ −1.5 °C/mod). We also measured the ability of **12** to stabilize oligonucleotides from 3′-exonuclease digestion by treating oligonucleotide **A7** with snake venom phosphodiesterase. We found that modification **12** can provide a significant improvement in nuclease stability relative to unmodified DNA oligonucleotide **A6** (Figure 3).

## ■ CONCLUSIONS

In conclusion, we report the synthesis and duplex-forming properties of oligonucleotides modified with *cis*-α-L-[4.3.0]-bicyclo-DNA monomer (**12**). Synthesis of the nucleoside phosphoramidite was accomplished in 23 steps starting from commercially available L-arabinose. The synthesis features the use of key diastereoselective C−C bond forming reactions, including a Sakurai allylation reaction and an intramolecular L-proline-catalyzed aldol reaction. Evaluation of oligonucleotides modified with **12** in UV-monitored thermal denaturation experiments revealed that this modification has a slight destabilizing effect upon oligonucleotide duplex formation. Structural analysis of modification **12** suggests that one conformation of the *cis*-fused bicyclic ring system is capable of orienting the nucleobase, 3′-OH, and the 5′-phosphodiester


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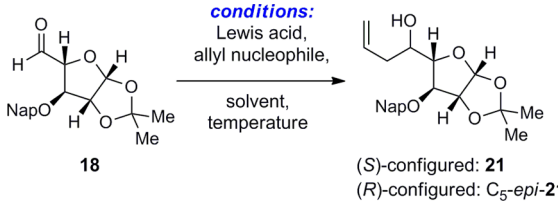
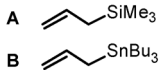
**Table 1. Optimization of Stereoselective Allylation Reactions of Common Aldehyde Precursor 18**




| entry | allyl source (amt (equiv))[a] | Lewis acid (amt (equiv)) | solvent/ temp (°C) | dr (21:C5-*epi*-21)[b] | isolated yield (%)[c] |
|---|---|---|---|---|---|
| 1 | A (1.75) | $BF_3{\cdot}OEt_2$ (2.0) | $CH_2Cl_2$/−78 | >20:1 | 86 |
| 2 | A (2.5) | $Ti_3CI_4$ (1.5) | $CH_2Cl_2$/−78 | decomp | |
| 3 | B (2.0) | $Ti_3CI_4$ (1.1) | $CH_2Cl_2$/−78 | 1:1 | 50 |
| 4 | B (1.5) | $ZnCI_4$ (1.1) | $CH_2$ $CI_2$/−78 | 5:1 | 82 |
| 5 | B (2.0) | $LiClO_4$ (5 M in $Et_2$ O) | $Et_2O$/25 | nr[e] | |
| 6 | A (2.0) | $MgBr_2{\cdot}OEt_2$ (1.1) | $CH_2Cl_2$/−78 | 1:1 | 86 |
| 7 | B (2.0) | $MgBr_2{\cdot}OEt_2$ (3.0) | $CH_2Cl_2$/−78 | 5:1 | 77 |
| 8 | B (2.0) | $MgBr_2{\cdot}OEt_2$ (3.0) | $CH_2Cl_2$/−78 | 1:4 | 93[d] |
| 9 | B (2.0) | $MgBr_2{\cdot}OEt_2$ (5.0) | $CH_2Cl_2$/−78 | 1:4 | 90 |
| 10 | B (2.0) | $MgBr_2{\cdot}OEt_2$ (3.0) | $CH_2Cl_2$/23 | 2:1 | 81 |

[a]

allyl nucleophile sources:



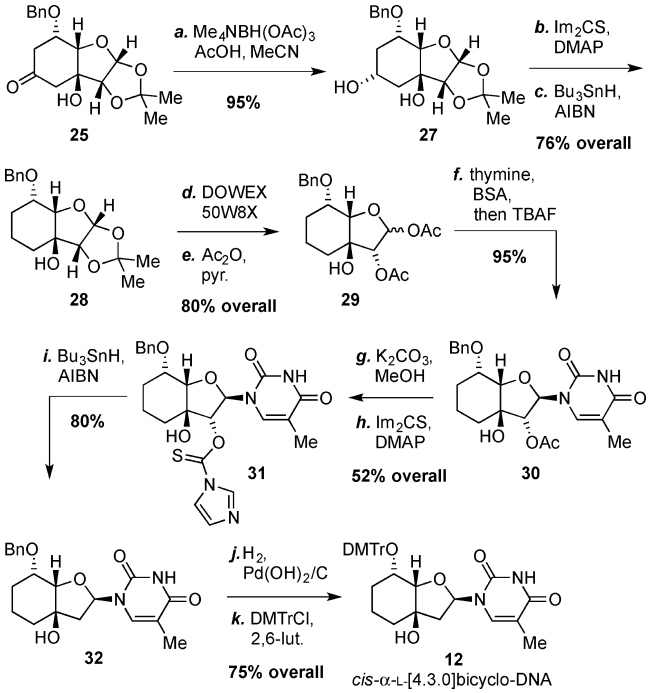

[b]dr was determined from the $^1$H NMR spectrum of the isolated mixture of **21** and C5-*epi*-**21**. [c]Isolated overall yield of **21** and **27**. [d]74% yield of **27** after chromatography. [e]nr = no reaction.

linkages in the same general orientation as those observed for α-L-LNA, while restricting rotation around the torsion angle γ. However, modification **12** lacks the 2′,4′-bridging substituent, which locks the furanose sugar ring of α-L-LNA in an N-type conformation. In the absence of structural data, it is difficult to predict if the destabilization produced by **12**, when incorporated into oligonucleotides **A2**, **A3**, and **A5**, is a consequence of the added steric bulk of the appended six-membered ring, the lack of a 2′,4′-bridging motif, or conformational mobility of the *cis*-fused ring system. Oligonucleotide **A7** harboring tandem incorporations of **12** provided a 285-fold improvement in nuclease stability relative to unmodified DNA. Further structural refinements of **12** to help dissect the contributions of these variables to oligonucleotide duplex stability are currently in progress.[35]

## EXPERIMENTAL SECTION

**General Procedures.** All nonaqueous reactions were run in an 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

**Scheme 3. Completion of the Synthesis of *cis*-α-L-[4.3.0]Bicyclo-DNA 12[a]**




[a]Conditions: (a) $Me_4NBH(OAc)_3$, AcOH, MeCN, 0−23 °C, 12 h; (b) $Im_2CS$, DMAP, $CH_2Cl_2$, 23 °C, 24 h; (c) $Bu_3SnH$, AIBN, PhMe, 110 °C, 30 min; (d) DOWEX 50W8X, $H_2O$/1,4-dioxane (1/1), 23 °C, 48 h; (e) $Ac_2O$, pyridine, 23 °C, 24 h; (f) thymine, BSA, MeCN, 80 °C, 1 h, then 0 °C, TMSOTf, 0−50 °C, 24 h, then TBAF, THF 23 °C, 30 min; (g). $K_2CO_3$, MeOH, 23 °C, 24 h; (h) $Im_2CS$, DMAP, $CH_2Cl_2$, 23 °C, 24 h; (i) $Bu_3SnH$, AIBN, PhMe, 110 °C, 1 h; (j) $H_2$, $Pd(OH)_2$/C, MeOH/THF (1/1), 23 °C, 24 h; (k) DMTrCl, 2,6-lutidine, pyridine/$CH_2Cl_2$ (1/1), 40 °C, 8 h.

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[36] 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 recorded at 300 or 400 MHz, calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$, δ 7.26 ppm; $CHD_2OD$, δ 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)-β-L-*arabino*-pentodialdofuranose (18).** Hünig's base (2.35 g, 18.2 mmol) and sulfur trioxide pyridine complex (2.89 g, 18.2 mmol), as a solution in DMSO (15 mL), were added sequentially to a stirred −20 °C solution of **20** (2.00 g, 6.05 mmol) in 9/1 dichloromethane/DMSO (54 mL). After 10 min, diethyl ether (100 mL) was added, followed by a 0 °C solution of brine (250 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The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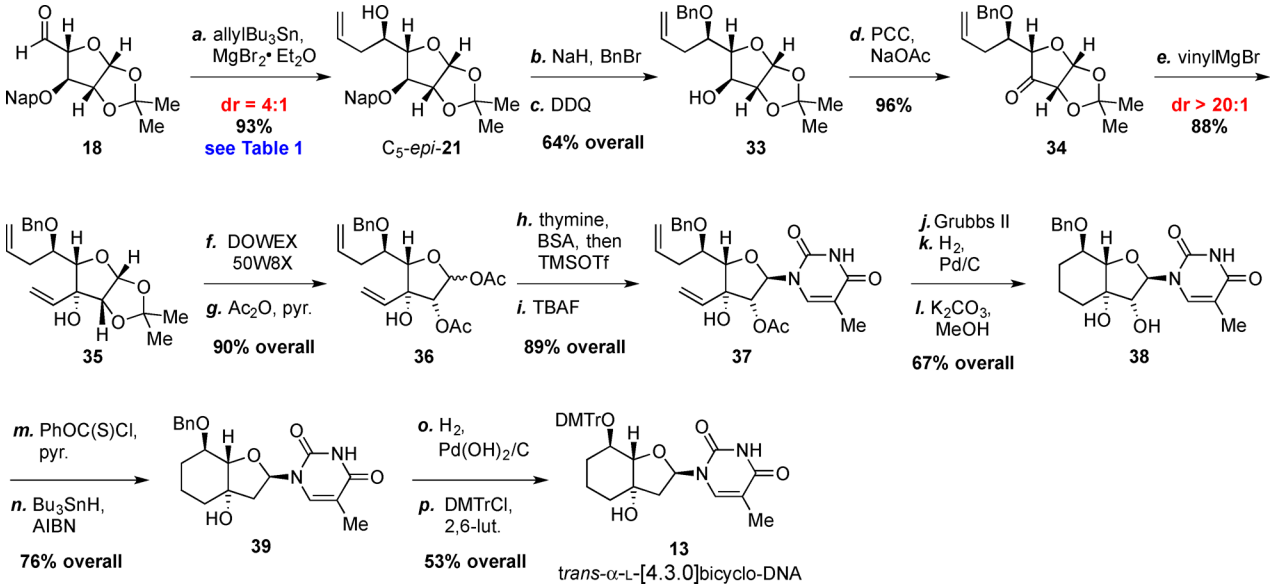
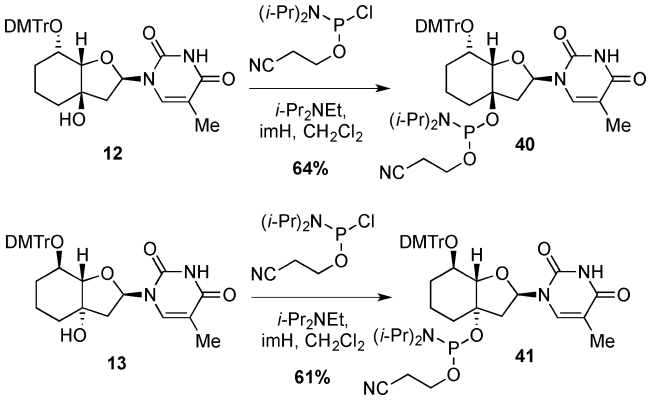
**Scheme 4. Synthesis of *trans*-α-L-[4.3.0]Bicyclo-DNA (13) from Common Aldehyde Precusor 18[a]**




[a]Conditions: (a) allyltributylstannane, $MgBr_2$ $Et_2O$, $CH_2Cl_2$, −78 °C, 3 h, dr = 4:1; (b) NaH, BnBr, TBAI, DMF/THF (1/1), 23 °C, 16 h; (c) DDQ, $H_2O/CH_2Cl_2$ (1/9), 23 °C, 4 h; (d) PCC, NaOAc, $CH_2Cl_2$, 23 °C, 16 h; (e) vinylmagnesium bromide, THF, 0 °C, 30 min; (f) DOWEX 50W8X, $H_2O$/1,4-dioxane (1/1), 50 °C, 12 h; (g) $Ac_2O$, pyridine, 0−23 °C, 18 h; (h) thymine, BSA, MeCN, 80 °C, 1 h, then 0 °C, TMSOTf, 0−50 °C, 24 h; (i) TBAF, THF, 23 °C, 30 min; (j) Grubbs second-generation catalyst (5 mol %), $CH_2Cl_2$, 23 °C, 1 h; (k) $H_2$, Pd/C, MeOH, 23 °C, 2 h; (l) $K_2CO_3$, MeOH, 23 °C, 12 h; (m) PhOC(S)Cl, pyridine/$CH_2Cl_2$ (1/1), 23 °C, 6 h; (n) $Bu_3SnH$, AIBN, PhMe, 110 °C, 30 min; (o) $H_2$, $Pd(OH)_2$/C, MeOH/THF (1/1), 23 °C, 24 h; (p) DMTrCl, 2,6-lutidine, pyridine/$CH_2Cl_2$ (1/1), 40 °C, 24 h.

**Scheme 5. Synthesis of Phosphoramidites 40 and 41 for Oligonucleotide Synthesis**




combined organic extracts were washed with 0.5 M HCl (3 × 100 mL), water (100 mL), and a saturated $NaHCO_3$ solution (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (50 mL) and concentrated under reduced pressure three times to remove residual amounts of pyridine. The resulting colorless oil was dried under high vacuum and used in further experiments without purification (1.87 g, 94%): $R_f$ = 0.30 (1:4 EtOAc/hexanes); $[\alpha]_D^{20}$ +13 (*c* 0.37, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.88−7.81 (m, 4H), 7.53−7.44 (m, 3H), 6.13 (d, *J* = 3.6 Hz, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.74 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 3.6 Hz, 1H), 4.60 (s, 1H), 4.41 (s, 1H), 1.47 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 201.8, 134.3, 133.3, 133.2, 129.2, 128.6, 128.4, 128.1, 127.9, 127.0, 126.5, 126.3, 125.7, 125.4, 112.3, 106.7, 88.9, 85.0, 83.0, 72.2, 26.3, 25.7; HRMS (ESI) calcd for $C_{19}H_{21}O_5$ $[M + H]^+$ *m*/*z* 329.1384, found 329.1380.

**1,2-*O*-Isopropylidene-3-*O*-(2-naphthylmethyl)-β-L-arabinofuranose (20).** A solution of **19**[24] (7.00 g, 16.3 mmol) in 1/1 DMF/THF (10 mL), and 2-(bromomethyl)naphthalene (4.32 g, 19.6 mmol) were added to a stirred 0 °C slurry of NaH (60% dispersion in oil, 1.31 g, 32.7 mmol) and tetrabutylammonium iodide (3.01 g, 8.15 mmol) in

**Table 2. Sequence, Analytical Data, Duplex Stabilizing Properties, and Nuclease Stability Profile of Modified Oligonucleotides**

| ODN | mod | mass calcd | mass found | sequence (5′ to 3′)[a] | $\Delta T_m$/mod (°C) vs RNA[b] | $\Delta T_m$/mod (°C) vs DNA[b] | $T_{1/2}$ (min) |
|---|---|---|---|---|---|---|---|
| **A1** | DNA[c] | 3633.4 | 3632.9 | d(GCGTTTTTTGCT) | control | control | |
| **A2** | **12** | 3673.4 | 3672.9 | d(GCGTT**T**TTTGCT) | −3.7 | −8.8 | |
| **A3** | **12** | 3713.5 | 3713.0 | d(GCGTT**TT**TTGCT) | −2.9 | −7.6 | |
| **A4** | DNA[c] | 3645.2 | 3645.5 | d(CCAGTGATATGC) | control | control | |
| **A5** | **12** | 3765.6 | 3765.1 | d(CCAG**T**GA**T**A**T**GC) | −1.5 | −4.6 | |
| **A6** | DNA[c] | 3588.4 | 3588.0 | d(TTTTTTTTTTTT) | | | 0.22 |
| **A7** | **12** | 3668.5 | 3668.0 | d(TTTTTTTTTTT**TT**) | | | 62.7 |

[a]Bold and underlined letters indicates modified nucleotide. Base code: T = thymine, U = uracil, C = cytosine, A = adenine, 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 RNA complement 5′-r(AGCAAAAAACGC)-3′ for **A1**−**A3** and 5′-r(GCAUAUCACUGG)-3′ for **A4** and **A5**. Sequence of DNA complement 5′-d(AGCAAAAAACGC)-3′ for **A1**−**A3** and 5′- d(GCAUAUCACUGG)-3′ for **A4** and **A5**. [c]DNA oligonucleotides were purchased from commercial vendors and used as supplied.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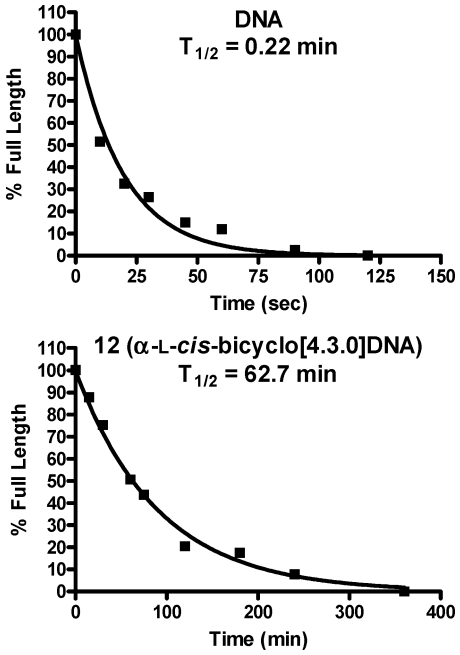


**Figure 3.** Nuclease stability profiles of oligonucleotides **A6** (top) and **A7** (bottom) after incubation with snake venom phosphodiesterase.

1/1 DMF/THF (90 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 2 h, the reaction mixture was cooled to 0 °C and methanol (2 mL), diethyl ether (250 mL), and water (100 mL) were added sequentially. The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (26 × 3 cm; 1/9 EtOAc/hexanes) to afford the 3-Nap ether as a colorless oil (7.78 g, 84%): $R_f$ = 0.31 (1/9 EtOAc/hexanes); $[\alpha]_D^{20}$ +5.7 (*c* 0.87, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.88–7.80 (m, 4H), 7.74–7.66 (m, 4H), 7.52–7.37 (m, 9H), 6.03 (d, *J* = 4.0 Hz, 1H), 4.89 (d, *J* = 12.0 Hz, 1H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.82 (d, *J* = 4.0 Hz, 1H), 4.43–4.38 (m, 2H), 4.00–3.92 (m, 2H), 1.46 (s, 3H), 1.40 (s, 3H), 1.14 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 135.7, 135.1, 133.40, 133.35, 133.2, 129.90, 129.84, 128.5, 128.1, 127.89, 127.85, 126.7, 126.3, 126.1, 125.8, 112.6, 105.9, 85.4, 85.3, 82.9, 77.4, 71.9, 63.6, 27.1, 26.9, 26.3, 19.3; HRMS (ESI) calcd for $C_{35}H_{44}NO_5Si$ $[M + NH_4]^+$ *m*/*z* 586.2983, found 586.2995. Tetrabutylammonium fluoride (1.0 M in THF, 7.3 mL, 7.3 mmol) was added to a stirred solution of the ether (3.75 g, 6.59 mmol) in THF (50 mL). After 4 h, a saturated solution of $NaHCO_3$ (10 mL) was added and the resulting mixture was further diluted with EtOAc (200 mL). The layers were separated and the organic phase was washed with a saturated solution of $NaHCO_3$ (100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (21 × 2 cm; 1:2 EtOAc/hexanes) to give **20** as a colorless oil (2.03 g, 93%): $R_f$ = 0.55 (1:1 EtOAc/hexanes); $[\alpha]_D^{20}$ −8.0 (*c* 1.7, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.89–7.81 (m, 4H), 7.54–7.46 (m, 3H), 5.98 (d, *J* = 4.4 Hz, 1H), 4.84–4.74 (m, 3H), 4.31–4.26 (m, 1H), 4.08–4.04 (m, 1H), 3.81–3.75 (m, 2H), 2.29 (br s, 1H), 1.56 (s, 3H), 1.38 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 134.7, 133.2, 133.1, 128.3, 127.9, 127.7, 126.6, 126.2, 126.1, 125.6, 112.8, 105.6, 85.7, 85.2, 82.8, 77.4, 71.8, 62.6, 27.1, 26.3; HRMS (ESI) calcd for $C_{19}H_{22}O_5Na$ $[M + Na]^+$ *m*/*z* 353.1359, found 353.1368.

**1,2-*O*-Isopropylidene-3-*O*-(2-naphthylmethyl)-6-deoxy-6-*C*-vinyl-β-L-altrofuranose (21).** Boron trifluoride diethyl etherate was added to a stirred −78 °C solution of aldehyde **18** (3.75 g, 11.4 mmol) in dichloromethane (200 mL). After 5 min, allyltrimethylsilane (2.28 g, 20.0 mmol) was added and the resulting solution was stirred at −78 °C for 3 h. The reaction mixture was poured directly into a 0 °C solution of saturated $NaHCO_3$ (100 mL) and further diluted with dichloromethane (100 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25 × 2 cm; 1/5 EtOAc/hexanes) to give **21** as a colorless solid (3.63 g, 86%): $R_f$ = 0.42 (1:4 EtOAc/hexanes); mp 74–78 °C; $[\alpha]_D^{20}$ −3.4 (*c* 1.7, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.86–7.82 (m, 4H), 7.52–7.48 (m, 3H), 6.00 (d, *J* = 3.9 Hz, 1H), 5.98–5.87 (m, 1H), 5.21–5.15 (m, 2H), 4.81 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 4.72 (d, *J* = 3.9 Hz, 1H), 4.33 (d, *J* = 2.4 Hz, 1H), 4.06 (dd, *J* = 4.2, 2.7 Hz, 1H), 3.95–3.89 (m, 1H), 2.55–2.47 (m, 1H), 2.28–2.18 (m, 1H), 1.56 (s, 3H), 1.38 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 134.9, 134.3, 133.4, 133.2, 128.5, 128.1, 127.9, 127.0, 126.4, 126.2, 125.9, 118.7, 112.9, 105.8, 87.9, 85.5, 82.6, 77.6, 72.0, 70.2, 37.8, 27.4, 26.5; HRMS (ESI) calcd for $C_{22}H_{26}O_5Na$ $[M + Na]^+$ *m*/*z* 393.1673, found 393.1679.

**1,2-*O*-Isopropylidene-5-*O*-benzyl-6-deoxy-6-*C*-vinyl-β-L-altrofuranose (22).** Sodium hydride (60% dispersion in oil, 0.130 g, 3.24 mmol), benzyl bromide (0.831 g, 4.86 mmol), and tetrabutylammonium iodide (0.120 g, 0.324 mmol) were added sequentially to a stirred 0 °C solution of **21** (0.600 g, 1.62 mmol) in 1/1 DMF/THF (20 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 2 h, the reaction mixture was cooled to 0 °C and methanol (2 mL), diethyl ether (100 mL), and water (100 mL) were added sequentially. The layers separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (19 × 2 cm; 1/9 EtOAc/hexanes) to give the benzyl ether as a colorless oil (0.728 g, 98%): $R_f$ = 0.70 (1/3 EtOAc/hexanes); $[\alpha]_D^{20}$ +23 (*c* 1.2, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.90–7.81 (m, 4H), 7.56–7.49 (m, 3H), 7.43–7.31 (m, 5H), 6.13–5.97 (m, 2H), 5.34–5.21 (m, 2H), 4.85–4.73 (m, 4H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.29–4.23 (m, 2H), 3.87–3.81 (m, 1H), 2.75–2.68 (m, 1H), 2.61–2.51 (m, 1H), 1.54 (s, 3H), 1.39 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 138.3, 135.1, 134.1, 133.4, 133.2, 128.44, 128.36, 128.1, 128.0, 127.8, 127.7, 126.8, 126.2, 126.1, 125.9, 118.0, 112.3, 106.1, 86.0, 85.1, 82.8, 77.6, 72.1, 71.5, 34.8, 27.0, 26.1; HRMS (ESI) calcd for $C_{29}H_{36}O_5N$ $[M + NH_4]^+$ *m*/*z* 478.2588, found 478.2599. DDQ (1.66 g, 7.32 mmol) was added to a vigorously stirred solution of the above ether (1.68 g, 3.66 mmol) in 1/9 water/dichloromethane (100 mL). After 6 h, a 10% solution of $NaHSO_3$ (100 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (24 × 2 cm; 1/3 EtOAc/hexanes) to afford **22** as a colorless oil (0.931 g, 79%): $R_f$ = 0.16 (1:4 EtOAc/hexanes); $[\alpha]_D^{20}$ +43 (*c* 1.4, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.36–7.29 (m, 5H), 5.98–5.88 (m, 1H), 5.87 (d, *J* = 4.0 Hz, 1H), 5.21–5.12 (m, 2H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.53–4.48 (m, 2H), 4.34–4.31 (m, 1H), 3.82 (dd, *J* = 6.4, 2.8 Hz, 1H), 3.77–3.72 (m, 1H), 2.65–2.58 (m, 1H), 2.45–2.38 (m, 1H), 2.22 (d, *J* = 3.6 Hz, 1H), 1.45 (s, 3H), 1.31 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 137.9, 133.6, 128.5, 128.1, 127.9, 118.1, 112.5, 105.5, 87.4, 86.8, 78.1, 76.8, 71.9, 34.6, 26.9, 26.2; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ $[M + Na]^+$ *m*/*z* 343.1516, found 343.1529.

**1,2-*O*-Isopropylidene-3-keto-5-*O*-benzyl-6-deoxy-6-*C*-vinyl-β-L-altrofuranose (23).** A solution of **22** (0.930 g, 2.90 mmol) in dichloromethane (20 mL) was added to a stirred 0 °C slurry of PCC (1.88 g, 8.70 mmol), anhydrous sodium acetate (0.726 g, 8.85 mmol), and 4 Å molecular sieves in dichloromethane (80 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 6 h, diethyl ether (100 mL) and silica gel (ca. 2 g)


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were added. The resulting mixture was filtered under vacuum through a short pad of silica gel (3 cm) and washed diethyl ether (100 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (22 × 2 cm; 1/4 EtOAc/hexanes) to afford **23** as a colorless oil (0.907 g, 98%): $R_f$ = 0.46 (1:3 EtOAc/hexanes); $[\alpha]_D^{20}$ +11 (*c* 0.42, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.28 (m, 5H), 6.01 (d, *J* = 4.0 Hz, 1H), 5.93−5.81 (m, 1H), 5.21−5.09 (m, 2H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 4.0 Hz, 1H), 4.21 (d, *J* = 5.6 Hz, 1H), 3.88−3.82 (m, 1H), 2.55−2.50 (m, 2H), 1.49 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 207.2, 138.0, 134.0, 128.4, 128.1, 127.8, 118.2, 114.9, 102.6, 81.3, 78.6, 77.0, 72.5, 35.1, 27.0, 26.7; HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ $[M + Na]^+$ *m*/*z* 341.1359, found 341.1364.

**1,2-*O*-Isopropylidene-3-keto-5-*O*-benzyl-6-deoxy-6-*C*-acetyl-*β*-L-altrofuranose (24).** $PdCl_2$ (0.156 g, 0.879 mmol) and $Cu(OAc)_2$ (0.319 g, 1.76 mmol) were added to a stirred solution of **23** (2.80 g, 8.79 mmol) in 7/1 DMA/$H_2O$ (77 mL). The reaction mixture was purged with a balloon of oxygen gas and subsequently maintained under an atmosphere of oxygen gas (via an oxygen-filled balloon). After 48 h, the reaction mixture was filtered through a pad of Celite. The filtrate was diluted with diethyl ether (200 mL) and water (100 mL), the layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (23 × 3 cm; 3/7 EtOAc/hexanes) to give **24** as a colorless oil (2.33 g, 79%): $R_f$ = 0.48 (1:2 EtOAc/hexanes); $[\alpha]_D^{20}$ −18.9 (c 1.11, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32−7.26 (m, 5H), 5.89 (d, *J* = 4.0 Hz, 1H), 4.68 (d, *J* = 11.2 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.35 (d, *J* = 4.4 Hz, 1H), 4.33−4.28 (m, 1H), 4.15 (d, *J* = 5.6 Hz, 1H), 2.92−2.87 (m, 1H), 2.76−2.68 (m, 1H), 2.09 (s, 3H), 1.46 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 207.0, 206.2, 137.9, 128.3, 128.1, 127.7, 115.0, 102.5, 81.5, 76.9, 75.2, 73.4, 45.1, 30.9, 26.9, 26.6; HRMS (ESI) calcd for $C_{18}H_{22}O_6Na$ $[M + Na]^+$ *m*/*z* 357.1309, found 357.1322.

**(3a*R*,4a*S*,5*S*,8a*S*,8b*R*)-5-(Benzyloxy)-8a-hydroxy-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*b*]benzofuran-7(4a*H*)-one (25).** L-Proline (0.109 g, 0.950 mmol) was added to a stirred solution of **24** (1.27 g, 3.80 mmol) in DMF (80 mL) at room temperature. After 3 days, the reaction mixture was diluted with diethyl ether (500 mL) and water (150 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 2 cm; 2/3 EtOAc/hexanes) to give **25** as a colorless oil (0.990 g, 78%). For an alternate procedure that involves heating the reaction in DMSO as solvent, see the Supporting Information, Table SI1: $R_f$ = 0.28 (1/1 EtOAc/hexanes); $[\alpha]_D^{20}$ −68 (*c* 0.87, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33−7.28 (m, 5H), 5.90 (d, *J* = 3.2 Hz, 1H), 4.71 (d, *J* = 12.4 Hz. 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.38 (d, *J* = 3.2 Hz, 1H), 4.14 (d, *J* = 4.0 Hz, 1H), 4.08−4.02 (m, 1H), 3.75 (s, 1H), 3.20 (d, *J* = 16.4 Hz, 1H), 2.69−2.60 (m, 1H), 2.41−2.32 (m, 2H), 1.44 (s, 3H), 1.28 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 208.9, 137.9, 128.5, 127.9, 127.8, 115.3, 104.6, 89.3, 84.9, 78.1, 77.4, 72.11, 71.6, 47.0, 39.8, 27.4, 27.0; HRMS (ESI) calcd for $C_{18}H_{22}O_6Na$ $[M + Na]^+$ *m*/*z* 357.1309, found 357.1325.

**1,2-*O*-Isopropylidene-3-*O*-(2-naphthylmethyl)-6-deoxy-6-*C*-vinyl-*α*-D-galactofuranose (*epi*-21).** Magnesium bromide diethyl etherate (14.9 g, 57.9 mmol) and allyltrimethylsilane (7.68 g, 23.2 mmol) were added to a stirred −78 °C solution of **18** (3.81 g, 11.6 mmol) in dichloromethane (100 mL) . After 2 h, the reaction mixture was poured into an ice-cold solution of saturated $NaHCO_3$ (200 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (32 × 3 cm; 1/4 EtOAc/hexanes) to give $C_5$-*epi*-**21** as a colorless oil (3.27 g, 76%): $R_f$ = 0.50 (3/7 EtOAc/hexanes); $[\alpha]_D^{20}$ −16.3 (*c* 1.32, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.87−7.79 (m, 4H), 7.51−7.44 (m, 3H), 5.97 (d, *J* = 4.0 Hz, 1H), 5.95−5.82 (m, 1H), 5.13−5.07 (m, 2H), 4.85 (d, *J* = 12.0 Hz, 1H), 4.77−4.70 (m, 2H), 4.08−4.02 (m, 2H), 3.83−3.77 (m, 1H), 2.52 (br s, 1H), 2.31−2.26 (m, 2H), 1.57 (s, 3H), 1.38 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 134.6, 134.3, 133.4, 133.3, 128.6, 128.1, 127.9, 126.9, 126.5, 126.3, 125.8, 117.8, 113.2, 105.6, 87.9, 85.4, 83.4, 72.2, 70.4, 38.3, 27.2, 26.6; HRMS (ESI) calcd for $C_{22}H_{26}O_5Na$ $[M + Na]^+$ *m*/*z* 393.1673, found 393.1678.

**(3a*R*,4a*S*,5*S*,7*R*,8a*S*,8b*R*)-5-(Benzyloxy)-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*b*]benzofuran-7,8a(4a*H*)-diol (27).** A solution of **25** (0.860 g, 2.57 mmol) in acetonitrile (15 mL) was added to a stirred 0 °C solution of $Me_4NBH(OAc)_3$ (3.38 g, 12.9 mmol) and acetic acid (1.54 g, 25.7 mmol) in acetonitrile (15 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 4 h, the reaction mixture was poured into water (100 mL) and diluted with EtOAc (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 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 (15 × 2 cm; 9/1 EtOAc/hexanes) to give **27** as a colorless foam (0.821 g, 95%): $R_f$ = 0.60 (EtOAc); $[\alpha]_D^{20}$ −1.5 (*c* 0.34, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.26 (m, 5H), 5.73 (d, *J* = 5.2 Hz, 1H), 4.60 (s, 2H), 4.48 (d, *J* = 5.2 Hz, 1H), 3.91 (d, *J* = 4.0 Hz, 1H), 3.86−3.80 (m, 1H), 3.68−3.64 (m, 1H), 3.14 (br s, 1H), 2.83 (br s, 1H), 2.18−2.11 (m, 1H), 1.91−1.72 (m, 3H), 1.57 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.2, 128.5, 127.9, 127.8, 115.8, 103.9, 89.3, 79.5, 78.4, 77.4, 73.0, 70.8, 65.8, 38.9, 35.2, 27.2, 26.8; HRMS (ESI) calcd for $C_{18}H_{24}O_6Na$ $[M + Na]^+$ *m*/*z* 359.1465, found 359.1472.

**(3a*R*,4a*S*,5*S*,8a*S*,8b*R*)-5-(Benzyloxy)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-*b*]benzofuran-8a(4a*H*)-ol (28).** 1,1′-Thiocarbonyldiimidazole (0.522 g, 2.92 mmol) and DMAP (0.030 g, 0.24 mmol) were added to a stirred solution of **27** (0.821 g, 2.44 mmol) in dichloromethane (25 mL). After 24 h, the reaction mixture was diluted with dichloromethane (100 mL) and water (100 mL). The layers were separated, and the organic phase was washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 2 cm; 2/1 EtOAc/hexanes) to give the thiocarbonyl imidazole ester as a colorless foam (1.01 g, 93%): $R_f$ = 0.33 (2:1 EtOAc/hexanes); $[\alpha]_D^{20}$ +11 (*c* 0.38, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.35 (s, 1H), 7.58 (s, 1H), 7.36−7.22 (m, 5H), 7.00 (s, 1H), 5.80 (d, *J* = 4.8 Hz, 1H), 5.72−5.65 (m, 1H), 5.21 (br s, 1H), 4.65 (s, 2H), 4.59 (d, *J* = 5.2 Hz, 1H), 4.01 (d, *J* = 3.6 Hz, 1H), 3.87−3.82 (m, 1H), 2.46−2.41 (m, 1H), 2.23−2.07 (m, 3H), 1.57 (s, 3H), 1.34 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 183.0, 137.91, 137.2, 130.2, 129.1, 128.5, 128.3, 127.9, 127.8, 125.4, 117.9, 115.8, 104.1, 89.3, 80.3, 79.0, 78.0, 72.2, 71.2, 34.4, 31.0, 27.1, 26.9 HRMS (ESI) calcd for $C_{22}H_{27}N_2O_6S$ $[M + H]^+$ *m*/*z* 447.1584, found 447.1597. A solution of tributyltin hydride (0.370 g, 1.27 mmol) and AIBN (0.010 mg, 0.042 mmol) in toluene (2 mL) was added dropwise to a stirred 110 °C solution of the above ester (0.189 g, 0.423 mmol) in toluene (20 mL). After 15 min, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (16 × 1 cm; 1/2 EtOAc/hexanes) to give **28** as a colorless oil (0.115 g, 85%): $R_f$ = 0.66 (3:2 EtOAc/hexanes); $[\alpha]_D^{20}$ −4.0 (*c* 0.10, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.28 (m, 5H), 5.76 (d, *J* = 5.2 Hz, 1H), 4.65−4.58 (m, 2H), 4.52 (d, *J* = 4.8 Hz, 1H), 3.98 (d, *J* = 3.6 Hz, 1H), 3.62−3.56 (m, 1H), 1.94−1.64 (m, 4H), 1.58 (s, 3H), 1.52−1.41 (m, 2H), 1.33 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 138.7, 128.5, 127.9, 127.7, 115.6, 104.0, 89.3, 80.6, 78.8, 74.6, 70.5, 29.7, 27.2, 26.7, 25.7, 19.6; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ $[M + Na]^+$ *m*/*z* 343.1516, found 343.1521.

**(3*R*,3a*S*,7*S*,7a*S*)-7-(Benzyloxy)-3a-hydroxyoctahydrobenzofuran-2,3-diyl Diacetate (29).** DOWEX 50W-8X ionic exchange resin (0.450 g) was added to a stirred solution of **28** (0.463 g, 1.45 mmol) in 1/1 dioxane/$H_2O$ (10 mL). After 3 days, the reaction mixture was filtered through a sintered-glass crucible, which was


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washed with water (50 mL) and EtOAc (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (16 × 1 cm; EtOAc) to give the hemiacetal as a colorless solid (0.386 g, 95%). Acetic anhydride (1.93 g, 18.9 mmol) was added to a stirred 0 °C solution of the hemiacetal (0.386 g, 1.38 mmol) in pyridine (30 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 16 h, the reaction mixture was diluted with EtOAc (50 mL) and poured into ice water (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with 0.5 M HCl (3 × 100 mL), water (100 mL), a saturated solution of $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (25 × 2 cm; 1/2 EtOAc/hexanes) to give **29** as a colorless oil (0.421 g, 86%): $R_f$ = 0.68 (2/1 EtOAc/hexanes); $[\alpha]_D^{20}$ −72 (*c* 0.071, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.34−7.22 (m, 5H), 6.21 (d, *J* = 3.6 Hz, 1H), 4.94 (d, *J* = 3.2 Hz, 1H), 4.64−4.55 (m, 2H), 4.37 (d, *J* = 3.2 Hz, 1H), 3.69 (s, 1H), 3.61−3.54 (m, 1H), 2.11 (s, 3H), 2.06 (s, 3H), 1.84−1.77 (m, 1H), 1.66−1.47 (m, 4H), 1.31−1.24 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 172.9, 169.8, 138.5, 128.4, 127.7, 127.6, 98.7, 88.9, 79.8, 79.2, 77.4, 74.4, 70.5, 28.6, 25.3, 21.3, 20.5, 19.3; HRMS (ESI) calcd for $C_{19}H_{24}O_7Na$ $[M + Na]^+$ *m*/*z* 387.1414, found 387.1421.

**(2*R*,3*R*,3a*S*,7*S*,7a*S*)-7-(Benzyloxy)-3a-hydroxy-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)octahydrobenzofuran-3-yl Acetate (30).** *N*,*O*-Bis(trimethylsilyl)acetamide (1.66 g, 8.15 mmol) was added to a stirred slurry of thymine (0.411 g, 3.25 mmol) in anhydrous acetonitrile (40 mL). The mixture was heated to 80 °C for 1 h and cooled to 0 °C, and a solution of **29** (0.593 g, 1.63 mmol) in acetonitrile (10 mL) was added, followed by the addition of TMSOTf (0.722 g, 3.25 mmol). The resulting mixture was heated to 50 °C for 12 h, cooled to 0 °C, and treated with a saturated solution of $NaHCO_3$ (1 mL). Ethyl acetate (250 mL) and a saturated solution of $NaHCO_3$ (100 mL) were added and the layers separated. The aqueous phase was extracted with EtOAc (3 × 100 mL), and the combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dried under high vacuum for 30 min and then dissolved in THF (10 mL). TBAF (1.0 M in THF, 2.5 mL, 2.5 mmol) was added, and the resulting solution was stirred at room temperature. After 30 min, ethyl acetate (50 mL) and a saturated solution of $NaHCO_3$ (50 mL) were added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 1.5 cm; 1/1 EtOAc/hexanes) to give **30** as a colorless foam (0.582 g, 83%): $R_f$ = 0.34 (1/1 EtOAc/hexanes); $[\alpha]_D^{20}$ −56 (*c* 1.2, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.08 (br s, 1H), 7.36−7.28 (m, 5H), 7.09 (d, *J* = 1.2 Hz, 1H), 5.82 (d, *J* = 5.6 Hz, 1H), 5.36 (d, *J* = 6.0 Hz, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.59 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 3.2 Hz, 1H), 3.87 (br s, 1H), 3.70−3.64 (m, 1H), 2.13 (s, 3H), 1.91 (s, 3H), 1.88−1.85 (m, 1H), 1.79−1.74 (m, 1H), 1.72−1.49 (m, 5H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.3, 163.6, 150.4, 138.2, 136.7, 128.4, 127.70, 127.66, 111.6, 89.5, 85.2, 81.4, 78.2, 74.9, 70.8, 29.1, 25.4, 20.5, 19.0, 12.6; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_7Na$ $[M + Na]^+$ *m*/*z* 453.1632, found 453.1643.

***O*-((2*R*,3*R*,3a*S*,7*S*,7a*S*)-7-(Benzyloxy)-3a-hydroxy-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)octahydrobenzofuran-3-yl) 1*H*-Imidazole-1-carbothioate (31).** Potassium carbonate (0.022 g, 0.16 mmol) was added to a stirred solution of **30** (0.690 g, 1.60 mmol) in MeOH (10 mL). After 18 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (50 mL). Water (50 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (4 × 25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a colorless foam (0.597 g, 96%), which was used without further purification: $R_f$ = 0.18 (3/1 EtOAc/hexanes); $[\alpha]_D^{20}$ −53 (*c* 0.45, $CHCl_3$); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.50 (d, *J* = 1.2 Hz, 1H), 7.36−7.25 (m, 5H), 5.68 (d, *J* = 6.4 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 2.8 Hz, 1H), 4.37 (d, *J* = 6.4 Hz, 1H), 3.71−3.64 (m, 1H), 1.90 (s, 3H), 1.81−1.57 (m, 6H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 166.5, 152.6, 139.8, 139.7, 129.5, 129.1, 128.8, 111.6, 93.0, 82.2, 81.5, 79.3, 77.0, 71.6, 29.4, 26.9, 20.4, 12.4; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_6$ $[M + H]^+$ *m*/*z* 389.1707, found 389.1722. 1,1′-Thiocarbonyl imidazole (0.114 g, 0.639 mmol) and DMAP (6 mg, 0.049 mmol) were added to a stirred 0 °C solution of the alcohol (0.191 g, 0.491 mmol) in dichloromethane (12 mL). The cooling bath was removed, and the resulting solution was warmed to room temperature. After 18 h, the reaction mixture was diluted with dichloromethane (50 mL) and the resulting solution was washed with water (100 mL), a saturated solution of $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (17 × 1.5 cm; 4/1 EtOAc/hexanes) to give **31** as a colorless foam (0.224 g, 92%): $R_f$ = 0.23 (4/1 EtOAc/hexanes); $[\alpha]_D^{20}$ −37 (*c* 0.17, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.18 (s, 1H), 8.30 (s, 1H), 7.46 (s, 1H), 7.35−7.29 (m, 6H), 7.11 (s, 1H), 6.92 (s, 1H), 6.37 (d, *J* = 5.4 Hz, 1H), 5.72 (d, *J* = 5.1 Hz, 1H), 5.36 (br s, 1H), 4.68−4.57 (m, 2H), 3.77−3.70 (m, 1H), 1.88 (s, 3H), 1.84−1.57 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 183.4, 164.2, 150.7, 138.0, 137.9, 137.1, 130.4, 128.4, 128.3, 127.8, 127.7, 117.8, 111.4, 90.5, 89.6, 81.3, 78.9, 74.7, 71.0, 29.7, 25.5, 19.1, 12.5; HRMS (ESI) calcd for $C_{24}H_{27}N_4O_6S$ $[M + H]^+$ *m*/*z* 499.1646, found 499.1650.

**1-((2*R*,3a*R*,7*S*,7a*S*)-7-(Benzyloxy)-3a-hydroxyoctahydrobenzofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (32).** Tributyltin hydride (0.231 g, 0.792 mmol) and AIBN (0.002 mg, 0.01 mmol), as a solution in toluene (2 mL), were added to a stirred a 110 °C of **31** (0.066 g, 0.132 mmol) in toluene (10 mL). After 30 min, the reaction mixture was concentrated under pressure and the residue was purified by flash chromatography (16 × 1 cm; 4/1 EtOAc/hexanes) to give **32** as a colorless oil (0.039 g, 80%): $R_f$ = 0.30 (4/1 EtOAc/hexanes); $[\alpha]_D^{20}$ +2.6 (*c* 0.31, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 10.53 (s, 1H), 7.68 (d, *J* = 1.2 Hz, 1H), 7.35−7.26 (m, 5H), 6.16 (dd, *J* = 5.4, 1.8 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 4.59 (d, *J* = 12.6 Hz, 1H), 4.18 (d, *J* = 4.8 Hz, 1H), 3.85−3.77 (m, 1H), 2.82−2.74 (m, 1H), 2.25 (d, *J* = 14.4 Hz, 1H), 2.03−1.95 (m, 1H), 1.92−1.86 (m, 1H), 1.81 (s, 3H), 1.65−1.58 (m, 2H), 1.41−1.32 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 164.5, 151.1, 138.4, 138.0, 128.4, 127.5, 127.3, 108.6, 87.8, 86.7, 75.2, 71.8, 43.8, 34.9, 26.6, 17.0, 12.4; HRMS (ESI) calcd for $C_{20}H_{24}N_2O_5Na$ $[M + Na]^+$ *m*/*z* 395.1577, found 395.1596.

**1-((2*R*,3a*R*,7*S*,7a*S*)-7-(Bis(4-methoxyphenyl)(phenyl)-methoxy)-3a-hydroxyoctahydrobenzofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (12).** Pearlman's catalyst (0.015 g, 0.022 mmol) was added to a stirred solution of **32** (0.169 g, 0.45 mmol) in 1/1 THF/MeOH (10 mL). A balloon filled with hydrogen gas was placed over the reaction mixture, and after 24 h, EtOAc (5 mL) and MeOH (5 mL) were added. The resulting slurry was filtered through a short pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 1/1 pyridine/dichloromethane (4 mL), and DMTrCl (0.41 g, 1.2 mmol) and 2,6-lutidine (0.13 g, 1.2 mmol) were added. The resulting solution was stirred and heated to 40 °C. After 24 h, dichloromethane (10 mL) was added and the resulting solution was washed with a saturated solution of sodium bicarbonate (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give *cis*-α-L-[4.3.0]bc-DNA (**12**) as a solid (0.20 g, 75% over two steps), which was used directly in the next step: $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 10.15 (s, 1H), 7.68−7.41 (m, 7H), 7.39−7.20 (m, 3H), 6.96−6.87 (m, 4H), 6.20 (t, *J* = 7.0 Hz, 1H), 4.17 (s, 1H), 3.92−3.87 (m, 1H), 3.82 (s, 6H), 2.95 (s, 1H), 2.47 (dd, *J* = 12.9, 6.8 Hz, 1H), 2.13−2.03 (m, 1H), 1.95 (d, *J* = 1.2 Hz, 3H), 1.66−1.58 (m, 2H), 1.51−1.40 (m, 2H), 1.35−1.29 (m, 1H), 1.13−1.03 (m, 1H); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 164.5, 159.6, 151.3, 147.4, 138.0, 137.9, 136.7, 131.3, 131.2, 129.3, 128.4, 127.5, 113.8, 113.7, 110.6, 87.3, 85.3, 84.5, 78.1, 71.8, 55.5, 46.7, 34.6, 27.8,


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20.5, 12.9; LRMS (ESI) calcd for $C_{34}H_{36}N_2O_7Na$ $[M + Na]^+$ $m/z$ 607.2, found 607.3.

**1,2-*O*-Isopropylidene-5-*O*-benzyl-6-deoxy-6-*C*-vinyl-α-D-galactofuranose (33).** Sodium hydride (60% dispersion in oil, 0.456 g, 11.4 mmol), benzyl bromide (1.95 g, 11.4 mmol), and tetrabutylammonium iodide (0.324 g, 0.877 mmol) were added to a stirred 0 °C solution of *epi*-**21** (3.25 g, 8.77 mmol) in 1/1 DMF/THF (100 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 4 h, the reaction mixture was cooled to 0 °C and MeOH (5 mL) was added, followed by diethyl ether (300 mL) and water (100 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (21 × 2 cm; 1/9 EtOAc/hexanes) to give the corresponding benzyl ether as a colorless oil (3.68 g, 91%): $R_f$ = 0.56 (1/4 EtOAc/hexanes); $[\alpha]_D^{20}$ −30 (*c* 0.89, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88−7.81 (m, 4H), 7.53−7.46 (m, 3H), 7.31−7.28 (m, 5H), 5.96−5.85 (m, 2H), 5.14−5.08 (m, 2H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.75 (dd, *J* = 3.2, 1.2 Hz, 1H), 4.66−4.63 (m, 2H), 4.57 (d, *J* = 11.6 Hz, 1H), 4.09−4.05 (m, 2H), 3.67−3.62 (m, 1H), 2.46−2.41 (m, 2H), 1.56 (s, 3H), 1.44 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 138.4, 134.52, 134.47, 133.1, 133.0, 128.2, 128.1, 127.9, 127.8, 127.6, 127.4, 126.9, 126.2, 126.0, 125.8, 117.3, 113.5, 104.7, 85.9, 84.8, 82.5, 77.7, 72.7, 71.9, 35.6, 27.4, 27.0; HRMS (ESI) calcd for $C_{29}H_{32}O_5Na$ $[M + Na]^+$ $m/z$ 483.2142, found 483.2138. DDQ (2.71 g, 11.9 mmol) was added to a vigorously stirred solution of the above product (2.75 g, 5.96 mmol) in 9/1 dichloromethane/water (70 mL). After 4 h, a 10% solution of $NaHSO_3$ (100 mL) was added and the layers were separated. The aqueous phase was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (24 × 2 cm; 3/7 EtOAc/hexanes) to give **33** as a colorless oil (1.34 g, 70%): $R_f$ = 0.13 (1/4 EtOAc/hexanes); $[\alpha]_D^{20}$ −9.2 (*c* 0.61, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 5.95−5.81 (m, 1H), 5.81 (d, *J* = 4.2 Hz, 1H), 5.17−5.06 (m, 2H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.48 (dd, *J* = 3.0, 1.2 Hz, 1H), 4.19−4.14 (m, 1H), 3.89−3.86 (m, 1H), 3.70−3.64 (m, 1H), 3.06 (d, *J* = 3.9 Hz, 1H), 2.45−2.29 (m, 2H), 1.49 (s, 3H), 1.32 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 138.3, 134.4, 128.2, 127.9, 127.5, 117.4, 113.1, 104.6, 87.6, 87.5, 77.9, 75.6, 72.8, 35.5, 27.1, 26.5; HRMS (ESI) calcd for $C_{18}H_{24}O_5Na$ $[M + Na]^+$ $m/z$ 343.1516, found 343.1525.

**1,2-*O*-Isopropylidene-3-keto-5-*O*-benzyl-6-deoxy-6-*C*-vinyl-α-D-galactofuranose (34).** A solution of **33** (2.54 g, 7.92 mmol), in dichloromethane (25 mL) was added to a stirred 0 °C solution of PCC (5.17 g, 24.0 mmol) and NaOAc (2.00 g, 24.3 mmol) in dichloromethane (100 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 3 h, silica gel (1 g) and diethyl ether (400 mL) were added. The resulting slurry was filtered through a short plug (3 cm) of silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (14 × 3 cm; 1/3 EtOAc/hexanes) to give **34** as a colorless oil (2.28 g, 90%): $R_f$ = 0.59 (3/7 EtOAc/hexanes); $[\alpha]_D^{20}$ −14 (*c* 0.73, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.33−7.23 (m, 5H), 6.01 (d, *J* = 4.5 Hz, 1H), 5.85−5.71 (m, 1H), 5.18−5.04 (m, 2H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 4.2 Hz, 1H), 4.15 (d, *J* = 4.5 Hz, 1H), 3.82−3.78 (m, 1H), 2.51−2.46 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 207.6, 137.8, 133.6, 128.0, 128.0, 127.4, 118.1, 115.1, 102.4, 82.9, 77.6, 76.9, 73.0, 34.9, 26.9, 26.8; HRMS (ESI) calcd for $C_{18}H_{22}O_5Na$ $[M + Na]^+$ $m/z$ 341.1359, found 341.1356.

**1,2-*O*-Isopropylidene-5-*O*-benzyl-6-deoxy-3,6-*C*-divinyl-α-D-gulofuranose (35).** Vinylmagnesium bromide (1.0 M solution in THF, 21 mL, 21 mmol) was added dropwise to a stirred 0 °C solution of **34** (2.28 g, 7.16 mmol) in anhydrous THF (100 mL). After 10 min, a saturated solution of $NH_4Cl$ (0.1 mL) was added, followed by EtOAc (100 mL) and an additional phase of a saturated solution of $NH_4Cl$ (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 × 50 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; 1/9 EtOAc/hexanes) to give **35** as a colorless oil (2.17 g, 88%): $R_f$ = 0.50 (1/9 EtOAc/hexanes); $[\alpha]_D^{20}$ +1.2 (*c* 0.26, MeOH); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.39−7.21 (m, 5H), 5.93−5.77 (m, 2H), 5.73 (d, *J* = 4.2 Hz, 1H), 5.46 (dd, *J* = 15.6, 1.2 Hz, 1H), 5.19 (dd, *J* = 9.3, 1.2 Hz, 1H), 5.12−5.03 (m, 2H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.33 (d, *J* = 4.2 Hz, 1H), 3.87−3.75 (m, 2H), 3.30 (s, 1H), 2.53−2.46 (m, 1H), 2.21−2.16 (m, 1H), 1.63 (s, 3H), 1.42 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.6, 134.6, 128.1, 127.9, 127.3, 117.1, 115.5, 114.5, 103.9, 87.1, 87.0, 78.0, 77.1, 73.0, 35.3, 27.5, 27.3; HRMS (ESI) calcd for $C_{20}H_{26}O_5Na$ $[M + Na]^+$ $m/z$ 369.1673, found 369.1671.

**1,2-*O*-Diacetyl-5-*O*-benzyl-6-deoxy-3,6-*C*-divinyl-D-gulofuranose (36).** DOWEX 50W-8X ionic exchange resin (1.50 g) was added to a stirred solution of **35** (1.75 g, 5.04 mmol) in 1/1 dioxane/water (10 mL). After 48 h, the reaction mixture was filtered through a sintered-glass crucible and the collected resin was washed with water (50 mL) and EtOAc (50 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (5 × 50 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a colorless oil, which was immediately dissolved in pyridine (40 mL), cooled to 0 °C, and stirred with acetic anhydride (4.24 g, 41.2 mmol). The cooling bath was remove,d and the reaction mixture was warmed to room temperature. After 16 h, EtOAc (100 mL) was added and the resulting mixture was poured into ice water (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20 × 2 cm; 1/3 EtOAc/hexanes) to give **36** as a colorless oil (dr = 6:1) (1.81 g, 92%) [major diastereomer]: $R_f$ = 0.50 (3/7 EtOAc/hexanes); $[\alpha]_D^{20}$ −109 (*c* 1.35, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 6.27 (d, *J* = 3.6 Hz, 1H), 5.85−5.74 (m, 2H), 5.49 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.52−5.10 (m, 4H), 4.71 (d, *J* = 11.2 Hz, 1H), 4.66 (s, 1H), 4.48 (d, *J* = 11.2 Hz, 1H), 4.08 (d, *J* = 2.8 Hz, 1H), 3.82−3.74 (m 1H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.08 (s, 3H), 2.05 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.5, 136.8, 136.6, 133.3, 128.5, 128.4, 128.1, 118.5, 117.1, 98.8, 82.7, 81.2, 80.7, 76.3, 71.8, 34.7, 21.1, 20.6; HRMS (ESI) calcd for $C_{21}H_{26}O_7Na$ $[M + Na]^+$ $m/z$ 413.1571, found 413.1563.

**1-(2-*O*-Acetyl-5-*O*-benzyl-6-deoxy-3,6-*C*-divinyl-β-D-gulofuranosyl)thymine (37).** *N*,*O*-Bis(trimethylsilyl)acetamide (4.50 g, 22.1 mmol) was added to a stirred slurry of thymine (1.12 g, 8.85 mmol) in anhydrous acetonitrile (70 mL), and the resulting mixture was heated to 80 °C. After 1 h, the reaction mixture was cooled to 0 °C and a solution of **36** (1.72 g, 4.42 mmol) in anhydrous acetonitrile (10 mL) and TMSOTf (1.97 g, 8.85 mmol) were added. The cooling bath was removed, and the reaction mixture was heated to 50 °C for 12 h, upon which a 0 °C solution of saturated $NaHCO_3$ (5 mL) was added. The resulting mixture was diluted with EtOAc (250 mL) and a saturated solution of $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dried under high vacuum for 30 min and dissolved in THF (50 mL), and TBAF (1.0 M in THF, 4.42 mL, 4.42 mmol) was added. The reaction mixture was stirred at room temperature for 30 min and then diluted with EtOAc (100 mL) and a saturated solution of $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 3 cm; 2/1 EtOAc/hexanes) to give nucleoside **37** as a colorless foam (1.80 g, 89%): $R_f$ = 0.48 (7/3 EtOAc/hexanes); $[\alpha]_D^{20}$ −64 (*c* 0.85, $CHCl_3$); $^1$H NMR


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(400 MHz, $CDCl_3$) $\delta$ 9.89 (br s, 1H), 7.36−7.28 (m, 5H), 7.04 (s, 1H), 5.92 (d, $J$ = 5.6 Hz, 1H), 5.86−5.75 (m, 2H), 5.69 (d, $J$ = 6.9 Hz, 1H), 5.53 (d, $J$ = 16.9 Hz, 1H), 5.31 (d, $J$ = 10.6 Hz, 1H), 5.19−5.11 (m, 2H), 4.97 (s, 1H), 4.71 (d, $J$ = 11.0 Hz, 1H), 4.52 (d, $J$ = 11.0 Hz, 1H), 4.42 (d, $J$ = 3.1 Hz, 1H), 3.87−3.82 (m, 1H), 2.53−2.47 (m, 2H), 2.06 (s, 3H), 1.90 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.3, 164.2, 150.7, 137.3, 136.8, 135.5, 133.3, 128.6, 128.6, 128.4, 128.3, 118.7, 118.3, 111.2, 89.9, 83.2, 80.9, 78.1, 76.8, 72.2, 34.9, 20.6, 12.5; HRMS (ESI) calcd for $C_{24}H_{32}N_3O_7$ $[M + NH_4]^+$ $m/z$ 474.2235, found 474.2240.

**1-((2*R*,3*R*,3a*S*,7*R*,7a*S*)-7-(Benzyloxy)-3,3a-dihydroxyoctahydrobenzofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (38).** Grubbs' second-generation catalyst (0.020 g, 0.024 mmol) was added to a stirred solution of **37** (0.440 g, 0.963 mmol) in dichloromethane (60 mL). The reaction mixture was heated to 40 °C for 20 min, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by flash chromatography (18 × 1.5 cm; 4/1 EtOAc/hexanes) to give a colorless foam (0.389 g, 94%): $R_f$ = 0.68 (9/1 EtOAc/hexanes); $[\alpha]_D^{20}$ −1.4 ($c$ 0.37, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.79 (s, 1H), 7.37−7.24 (m, 5H), 7.17 (s, 1H), 6.20 (d, $J$ = 6.6 Hz, 1H), 5.98 (d, $J$ = 9.6 Hz, 1H), 5.80−5.75 (m, 1H), 5.57 (d, $J$ = 6.6 Hz, 1H), 4.80 (d, $J$ = 5.57, 1H), 4.64 (d, $J$ = 12.0 Hz, 1H), 4.48−4.42 (m, 1H), 4.39−4.35 (m, 1H), 3.44 (s, 1H), 2.81−2.77 (m, 1H), 2.23−2.15 (m, 4H), 1.93 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.7, 164.3, 150.8, 138.5, 136.8, 132.0, 128.4, 127.9, 127.7, 127.6, 124.7, 111.6, 90.3, 86.2, 77.5, 77.0, 72.8, 72.1, 34.0, 20.8, 12.6; HRMS (ESI) calcd for $C_{22}H_{24}N_2O_7Na$ $[M + Na]^+$ $m/z$ 451.1476, found 451.1487. A solution of the above product (0.255 g, 0.595 mmol) in THF (5 mL) was added to a stirred slurry of 10% Pd/C (0.050 g) in THF (5 mL). The resulting slurry was purged with a balloon of hydrogen gas and then maintained under an atmosphere of hydrogen gas (balloon). After 2 h, the reaction mixture was diluted with ethyl acetate (10 mL) and filtered through a pad of Celite 545, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (19 × 1.5 9/1 EtOAc/hexanes) to give a colorless foam (0.183 g, 72%): $R_f$ = 0.55 (EtOAc); $[\alpha]_D^{20}$ +2.3 ($c$ 0.30, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.77 (s, 1H), 7.37−7.24 (m, 5H), 7.15 (s, 1H), 6.13 (d, $J$ = 6.4 Hz, 1H), 5.45 (d, $J$ = 6.4 Hz, 1H), 4.77 (d, $J$ = 12.0 Hz, 1H), 4.66 (d, $J$ = 12.0 Hz, 1H), 4.12 (d, $J$ = 9.2 Hz, 1H), 4.05−3.99 (m, 1H), 2.84 (s, 1H), 2.17−2.12 (m, 4H), 1.94 (s, 3H), 1.83−1.78 (m, 2H), 1.69−1.65 (m, 1H), 1.50−1.47 (m, 1H), 1.31−1.26 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.4, 164.2, 151.0, 138.8, 136.3, 128.4, 127.7, 127.6, 111.7, 89.3, 87.9, 79.4, 78.9, 77.4, 75.6, 72.0, 31.7, 30.5, 20.8, 19.7, 12.7; HRMS (ESI) calcd for $C_{22}H_{26}N_2O_7Na$ $[M + Na]^+$ $m/z$ 453.1632, found 453.1643. Potassium carbonate (0.0057 g, 0.042 mmol) was added to a stirred solution of the above product (0.180 g, 0.418 mmol) in MeOH (10 mL). After 6 h, the reaction mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (50 mL). Water (50 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (5 × 25 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (10 × 2 cm; EtOAc) to give nucleoside **38** as a colorless foam (0.160 g, 99%): $R_f$ = 0.40 (EtOAc); $[\alpha]_D^{20}$ −3.1 ($c$ 0.36, $CHCl_3$); $^1$H NMR (400 MHz, $CD_3OD$) $\delta$ 7.52 (d, $J$ = 1.2 Hz, 1H), 7.35−7.22 (m, 5H), 5.88 (d, $J$ = 6.8 Hz, 1H), 4.68 (d, $J$ = 11.6 Hz, 1H), 4.62 (d, $J$ = 11.6 Hz, 1H), 4.37 (d, $J$ = 6.8 Hz, 1H), 4.08 (d, $J$ = 9.6 Hz, 1H), 3.97−3.95 (m, 1H), 2.13−2.10 (m, 1H), 1.89 (s, 3H), 1.87−1.76 (m, 2H), 1.67−1.63 (m, 1H), 1.42−1.40 (m, 1H), 1.27−1.24 (m, 1H); $^{13}$C NMR (100 MHz, $CD_3OD$) $\delta$ 165.5, 151.8, 139.2, 138.8, 128.3, 127.9, 127.5, 110.9, 92.3, 87.4, 78.7, 78.5, 76.4, 71.8, 30.7, 30.5, 19.9, 11.3; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_6$ $[M + H]^+$ $m/z$ 389.1707, found 389.1712.

**1-((2*R*,3a*S*,7*R*,7a*S*)-7-(Benzyloxy)-3a-hydroxyoctahydrobenzofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (39).** *O*-Phenyl chlorothionoformate (0.360 g, 2.09 mmol) was added to a stirred −20 °C solution of **38** (0.162 g, 0.418 mmol) in 1/1 pyridine/dichloromethane (20 mL). The cooling bath was removed, and the reaction mixture was warmed to room temperature. After 6 h, the reaction mixture was diluted with dichloromethane (50 mL) and the resulting solution was washed with water (100 mL), a saturated solution of $NaHCO_3$ (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (17 × 1.5 cm; 3/2 EtOAc/hexanes) to give a colorless oil (0.224 g, 92%): $R_f$ = 0.50 (2/1 EtOAc/hexanes); $[\alpha]_D^{20}$ +1.1 ($c$ 0.18, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.53 (s, 1H), 7.40−7.25 (m, 8H), 7.13−7.09 (m, 3H), 6.27 (d, $J$ = 6.4 Hz, 1H), 6.16 (d, $J$ = 6.4 Hz, 1H), 4.78 (d, $J$ = 12.0 Hz, 1H), 4.66 (d, $J$ = 12.0 Hz, 1H), 4.30 (d, $J$ = 9.2 Hz, 1H), 4.08−4.04 (m, 1H), 2.94 (s, 1H), 2.16−2.13 (m, 1H), 1.98 (m, 1H), 1.91 (s, 3H), 1.85−1.81 (m, 1H), 1.71−1.58 (m, 2H), 1.41−1.24 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 194.4, 164.3, 153.5, 150.7, 138.9, 137.4, 129.8, 128.4, 127.7, 127.6, 127.0, 121.7, 111.6, 90.5, 87.7, 86.3, 79.4, 77.4, 75.6, 72.0, 32.0, 30.4, 19.7, 12.6; HRMS (ESI) calcd for $C_{27}H_{29}N_2O_7S$ $[M + H]^+$ $m/z$ 525.1690, found 525.1696. A toluene (10 mL) solution of tributyltin hydride (1.10 g, 3.79 mmol) and AIBN (10 mg, 0.063 mmol) were added dropwise to a stirred 110 °C solution of the above product (0.330 g, 0.631 mmol) in toluene (65 mL). After 30 min, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (16 × 2 cm; 4/1 EtOAc/hexanes) to give nucleoside **39** as a colorless foam (0.196 g, 83%): $R_f$ = 0.21 (4/1 EtOAc/hexanes); $[\alpha]_D^{20}$ +40 ($c$ 0.12, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.03 (s, 1H), 7.37−7.25 (m, 6H), 6.44−6.39 (m, 1H), 4.77 (d, $J$ = 12.0 Hz, 1H), 4.65 (d, $J$ = 12.0 Hz, 1H), 3.95−3.92 (m, 1H), 3.73 (d, $J$ = 9.2 Hz, 1H), 3.22 (s, 1H), 2.70 (dd, $J$ = 7.6, 6.0 Hz, 1H), 2.15−2.11 (m, 1H), 1.98−1.85 (m, 6H), 1.67−1.64 (m, 1H), 1.41−1.39 (m, 1H), 1.25−1.22 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 164.4, 150.9, 139.0, 135.3, 128.4, 127.7, 127.6, 111.3, 89.7, 86.7 79.3, 76.2, 72.0, 46.0, 32.9, 30.7, 20.1, 12.8; HRMS (ESI) calcd for $C_{20}H_{24}N_2O_5Na$ $[M + Na]^+$ $m/z$ 395.1577, found 395.1578.

**1-((2*R*,3a*S*,7*R*,7a*S*)-7-(Bis(4-methoxyphenyl)(phenyl)-methoxy)-3a-hydroxyoctahydrobenzofuran-2-yl)-5-methylpyrimidine-2,4(1*H*,3*H*)-dione (13).** Pearlman's catalyst (0.031 g, 0.044 mmol) was added to a stirred solution of **39** (0.185 g, 0.497 mmol) in 1/1 THF/MeOH (20 mL). A balloon filled with hydrogen gas was placed over the reaction mixture, and after 24 h, EtOAc (10 mL) and MeOH (10 mL) were added. The resulting slurry was filtered through a short pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 1/1 pyridine/dichloromethane (8 mL) and DMTrCl (0.483 g, 1.43 mmol) and 2,6-lutidine (0.153 g, 1.43 mmol) were added. The resulting solution was stirred and heated to 40 °C. After 24 h, dichloromethane (20 mL) was added and the resulting solution was washed with a saturated solution of sodium bicarbonate (2 × 20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica column previously neutralized with $NEt_3$ (16 × 2 cm; 3/1 EtOAc/hexanes) to give *trans*-$\alpha$-L-[4.3.0]bc-DNA (**13**) as an orange solid (0.153 g, 53% over two steps), which was used directly in the next step: $R_f$ = 0.44 (3:1 EtOAc/hexanes); $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ 10.25 (s, 1H), 8.04 (s, 1H), 7.75 (d, $J$ = 1.0 Hz, 2H), 7.65(d, $J$ = 7.2 Hz, 4H), 7.56 (d, $J$ = 8.9 Hz, 4H), 7.50 (d, $J$ = 8.9 Hz, 4H), 7.32−7.19 (m, 6H), 6.88 (dd, $J$ = 9.0, 2.4 Hz, 8H), 6.42 (dd, $J$ = 7.6, 6.3 Hz, 2H), 4.27−4.09 (m, 4H), 3.99−3.87 (m, 2H), 3.80 (s, 6H), 3.79 (s, 6H), 2.54 (dd, $J$ = 13.1, 6.2 Hz, 2H), 2.22 (dd, $J$ = 13.1, 7.9 Hz, 2H), 1.98 (d, $J$ = 0.7 Hz, 6H), 1.85−1.79 (m, 2H), 1.57−1.13 (m, 10H); $^{13}$C NMR (75 MHz, acetone-$d_6$) $\delta$ 164.6, 159.43, 159.36, 151.4, 147.7, 138.5, 138.2, 136.7, 131.4, 131.4, 129.4, 128.2, 127.2, 113.5, 110.6, 88.8, 86.64, 86.57, 79.4, 79.1, 72.5, 55.39, 55.37, 46.4, 33.7, 32.8, 20.9, 12.8.

**(2*R*,3a*R*,7*S*,7a*S*)-7-(Bis(4-methoxyphenyl)(phenyl)methoxy)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-hexahydrobenzofuran-3a(4*H*)-yl 2-Cyanoethyl-*N*,*N*-diisopropylphosphoramidite (40).** 2-Cyanoethyl-*N*,*N*-diisopropylchlorophosphoramidite (0.16 mL, 0.68 mmol) was added to a stirred solution of nucleoside **12** (0.20 g, 0.34 mmol), diisopropylethylamine (0.13 mL, 0.68 mmol), and *N*-methylimidazole (2 drops) in $CH_2Cl_2$ (2 mL). After 1 h, the reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure.


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Purification by flash chromatography (15 × 2 cm; 2/1 EtOAc/hexanes) gave phosphoramidite **40** as a white foam (0.17 g, 64%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07 (br s, 1H), 7.62−7.14 (m, 17H), 6.81 (d, $J$ = 7.5 Hz, 5H), 6.01 (d, $J$ = 6.4 Hz, 1H), 3.90−3.36 (m, 14H), 2.88−2.44 (m, 4H), 2.21−1.88 (m, 6H), 1.50−1.34 (m, 3H), 1.32−0.77 (m, 23H); $^{31}$P NMR (121 MHz, $CDCl_3$) $\delta$ 143.0, 141.0; LRMS (ESI) calcd for $C_{43}H_{53}N_4O_8PNa$ $[M + Na]^+$ $m/z$ 785.4, found 785.4.

**(2*R*,3a*S*,7*R*,7a*S*)-7-(Bis(4-methoxyphenyl)(phenyl)methoxy)-2-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-hexahydrobenzofuran-3a(4*H*)-yl 2-Cyanoethyl-*N*,*N*-diisopropylphosphoramidite (41).** 2-Cyanoethyl-*N*,*N*-diisopropylchlorophosphoramidite (0.12 mL, 0.5 mmol) was added to a stirred solution of nucleoside **13** (0.15 g, 0.25 mmol), diisopropylethylamine (0.09 mL, 0.5 mmol), and *N*-methylimidazole (2 drops) in dichloromethane (1.5 mL). After 1 h, the reaction mixture was diluted with EtOAc (10 mL) and the organic layer was washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography (15 × 2 cm; 1/1 EtOAc/hexanes) gave phosphoramidite **41** as a white foam (0.12 g, 61%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.68−7.37 (m, 13H), 7.32−7.09 (m, 14H), 6.80 (d, $J$ = 6.4 Hz, 9H), 6.34 (br s, 1H), 6.25−6.08 (m, 1H), 4.14 (br s, 2H), 3.79 (br s, 23H), 3.64−3.30 (m, 9H), 3.22−3.04 (m, 1H), 2.75 (br s, 2H), 2.55 (br s, 3H), 2.05 (br s, 12H), 1.83 (d, $J$ = 6.6 Hz, 2H), 1.60 (br s, 22H), 1.31 (br s, 5H), 1.15−0.97 (m, 20H), 0.90 (d, $J$ = 5.7 Hz, 9H), 0.64 (br s, 2H); $^{31}$P NMR (121 MHz, $CDCl_3$) $\delta$ 142.3, 139.8; LRMS (ESI) calcd for $C_{43}H_{53}N_4O_8PNa$ $[M + Na]^+$ $m/z$ 785.4, found 785.4.

## ■ ASSOCIATED CONTENT

### Supporting Information

Figures, tables, and a CIF file giving compounds referred to in the Experimental Section (unnumbered in Schemes), temperature and solvent studies of the L-proline-catalyzed aldol reaction of **24**, $^1$H and $^{13}$C NMR spectra of new compounds, and crystallographic data for compound **26**. This material is 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) For representative reviews, see: (a) Campbell, M. A.; Wengel, J. *Chem. Soc. Rev.* **2011**, *40*, 5680−5689. (b) Lebreton, J.; Escudier, J.-M.; Arzel, L.; Len, C. *Chem. Rev.* **2010**, *110*, 3371−3418. (c) Kaur, H.; Babu, B. R.; Maiti, S. *Chem. Rev.* **2007**, *107*, 4672−4697.

(2) Bennett, C. F.; Swayze, E. E. *Annu. Rev. Pharmacol. Toxicol.* **2010**, *50*, 259−293.

(3) Obika, S.; Nanbu, D.; Hari, Y.; Andoh, J.-I.; Morio, K.-I.; Doi, T.; Imanishi, T. *Tetrahedron Lett.* **1998**, *39*, 5401−5404.

(4) Singh, S. K.; Nielsen, P.; Koshkin, A. A.; Wengel, J. *Chem Commun.* **1998**, 455−456.

(5) Jepsen, J. S.; Wengel, J. *Curr. Opin. Drug Discov. Devel.* **2004**, *7*, 188−194.

(6) Tarkov, M.; Bolli, M.; Leumann, C. J. *Helv. Chim. Acta* **1994**, *77*, 716−744.

(7) Tarkov, M.; Bolli, M.; Schweizer, B.; Leumann, C. J. *Helv. Chim. Acta* **1993**, *76*, 481−510.

(8) Tarkov, M.; Leumann, C. J. *Angew. Chem., Int. Ed.* **1993**, *32*, 1432−1434.

(9) Steffens, R.; Leumann, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3249−3255.

(10) Murray, S.; Ittig, D.; Koller, E.; Berdeja, A.; Chappell, A.; Prakash, T. P.; Norrbom, M.; Swayze, E. E.; Leumann, C. J.; Seth, P. P. *Nucleic Acids Res.* **2012**, *40*, 6135−6143.

(11) Pallan, P. S.; Ittig, D.; Héroux, A.; Wawrzak, Z.; Leumann, C. J.; Egli, M. *Chem. Commun.* **2008**, 883−885.

(12) Obika, S.; Sekiguchi, M.; Somjing, R.; Imanishi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 1944−1947.

(13) Osaki, T.; Obika, S.; Harada, Y.; Mitsuoka, Y.; Sugaya, K.; Sekiguchi, M.; Roongjang, S.; Imanishi, T. *Tetrahedron* **2007**, *63*, 8977−8986.

(14) Sekiguchi, M.; Obika, S.; Harada, Y.; Osaki, T.; Somjing, R.; Mitsuoka, Y.; Shibata, N.; Masaki, M.; Imanishi, T. *J. Org. Chem.* **2006**, *71*, 1306−1316.

(15) Shaikh, K. I.; Kumar, S.; Lundhus, L.; Bond, A. D.; Sharma, P. K.; Nielsen, P. *J. Org. Chem.* **2009**, *74*, 1557−1566.

(16) Stauffiger, A.; Leumann, C. J. *Eur. J. Org. Chem.* **2009**, 1153−1162.

(17) Rajwanshi, V. K.; Håkansson, A. E.; Sørensen, M. D.; Pitsch, S.; Singh, S. K.; Kumar, R.; Nielsen, P.; Wengel, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1656−1659.

(18) Sørensen, M. D.; Kvaerno, L.; Bryld, T.; Håkansson, A. E.; Verbeure, B.; Gaubert, G.; Herdewijn, P.; Wengel, J. *J. Am. Chem. Soc.* **2002**, *124*, 2164−2176.

(19) (a) Kumar, T. S.; Wengel, J.; Hrdlicka, P. J. *ChemBioChem.* **2007**, *8*, 1122−1125. (b) Kumar, T. S.; Madsen, A. S.; Østergaard, M. E.; Wengel, J.; Hrdlicka, P. J *J. Org. Chem.* **2008**, *73*, 7060−7066. (c) Kumar, T. S.; Madsen, A. S.; Østergaard, M. E.; Sau, S. P.; Wengel, J.; Hrdlicka, P. J. *J. Org. Chem.* **2009**, *74*, 1070−1081. (d) Li, Q.; Yuan, F.; Zhou, C.; Plashkevych, O.; Chattopadhyaya, J. *J. Org. Chem.* **2010**, *75*, 6122−6140. (e) Seth, P. P.; Allerson, C. R.; Berdeja, A.; Swayze, E. E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 588−591.

(20) (a) Seth, P. P.; Yu, J.; Allerson, C. R.; Berdeja, A.; Swayze, E. E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1122−1125. (b) Seth, P. P.; Allerson, C. A.; Østergaard, M. E.; Swayze, E. E. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4690−4694. (c) Seth, P. P.; Allerson, C. R.; Østergaard, M. E.; Swayze, E. E. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 296−299. (d) Seth, P. P.; Jazayeri, A.; Yu, J.; Allerson, C. R.; Bhat, B.; Swayze, E. E. *Mol. Ther. Nucleic Acids* **2012**, *1*, e47.

(21) Hanessian, S.; Schroeder, B. R.; Giacometti, R. D.; Merner, B. L.; Østergaard, M. E.; Swayze, E. E.; Seth, P. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 11242−11245.

(22) Petersen, M.; Håkansson, A. E.; Wengel, J.; Jacobsen, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 7431−7432.

(23) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496−497. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1619−1621.

(24) Génu-Dellac, C.; Gosselin, G.; Imbach, J.-L. *Carbohydr. Res.* **1991**, *216*, 249−255.

(25) (a) Danishefsky, S. J.; De Ninno, M. *Tetrahedron Lett.* **1985**, *26*, 823−824. (b) Danishefsky, S. J.; De Ninno, S. L.; Chen, S. H.; Boisvert, L.; Barbachyn, M. *J. Am. Soc.* **1989**, *111*, 5810−5818. See also: (c) Banuls, V.; Escudier, J. M. *Tetrahedron* **1999**, *55*, 5831−5838. (d) Sørensen, A. M.; Nielsen, P. *Org. Lett.* **2000**, *2*, 4217−4219. (e) Catana, D. A.; Maturano, M.; Payrastre, C.; Lavedan, P.; Tarrat, N.; Escudier, J. M. *Eur. J. Org. Chem.* **2011**, 2857−2863.

(26) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169−173.

(27) Smith, A. B.; Young, S. C.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.

(28) See the Supporting Information.

(29) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273−276. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(30) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(31) Niedballa, U.; Vorbrüggen, H. *Angew. Chem., Int. Ed.* **1970**, *9*, 461−462.
(32) Freitag, M.; Thomasen, H.; Christensen, N. K.; Petersen, M.; Neilsen, P. *Tetrahedron Lett.* **2004**, *60*, 3775−3786.
(33) 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.
(34) Seth, P.; Yu, J.; Jazayeri, A.; Pallan, P. S.; Allerson, C. R.; Østergaard, M. E.; Liu, F.; Herdewijn, P.; Egli, M.; Swayze, E. F. *J. Org. Chem.* **2012**, *77*, 5074−5085.
(35) See the following article for details: Hanessian, S.; Wagger, J.; Merner, B. L.; Giacometti, R. D.; Swayze, E. E.; Seth, P. *J. Org. Chem.* **2013**, DOI: 10.1021/jo401170y.
(36) Chromatography procedures and conditions were followed as described in: Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.