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Synthesis of Bicyclic 2′-Deoxynucleosides with α-L-*ribo*- and *β*-D-*xylo*-Configurations and Restricted *S*- and *N*-Type Conformations

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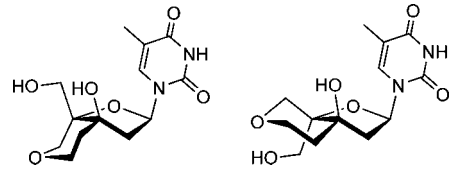

Two bicyclic 2′-deoxynucleoside analogues are synthesized in 12 steps each from thymidine. With a six-membered ring fused to the C3′−C4′ bond and an α-L-*ribo*- and a *β*-D-*xylo*-configuration, these are conformationally restricted in an *S*- and an *N*-type conformation, respectively. The constitutions were proven by X-ray crystallography. The *β*-D-*xylo*-configured analogue is successfully converted to a 3′-phosphoramidite and incorporated into oligodeoxynucleotides, which are found to hybridize to DNA and RNA complements with decreased affinity.

Introduction

The field of nucleic acid chemistry has developed tremendously by the introduction of conformationally restricted nucleoside building blocks.[1] Especially, nucleosides with bi- or tricyclic carbohydrate moieties have led to oligonucleotides with strong affinities for complementary DNA and RNA.[2] As a prime example, locked nucleic acid (LNA) has been introduced as oligonucleotides containing one or more of the [2.2.1]bicyclic nucleoside monomer **1**, which is conformationally locked in the *N*-type nucleoside conformation as a result of the additional 2′,4′-oxymethylene connection as compared to unmodified 2′-deoxynucleotides (Figure 1).[3] The introduction of one or more LNA monomers in an oligodeoxynucleotide (ODN) secures a conformational steering of neighboring 2′-deoxynucleotides toward the *N*-type conformation and formation of A-type or A-type-like duplexes with comple-

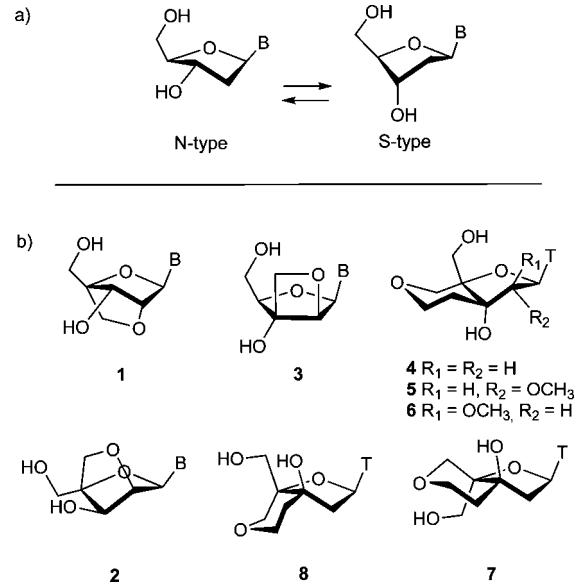

FIGURE 1. (a) Low-energy conformations of 2′-deoxynuclesides. (b) Conformationally restricted *β*-D- and α-L-configured bicyclic nucleosides. B = any nucleobase. T = thymin-1-yl.

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mentary RNA and DNA, respectively.[4] LNA has demonstrated unprecedented DNA- and RNA-recognition and promising results as potential antisense therapeutic compounds.[5]

Among a large number of chemical analogues of LNA, the stereoisomers of LNA have shown intriguing results.[6−10] α-L-LNA, **2**, has shown the same ability of significantly increasing duplex stability both in fully modified α-L-LNA sequences and in combination with unmodified naturally β-D-*ribo*-configured 2′-deoxynucleotides.[6,7] The resulting duplexes, however, are more B-type-like duplexes with the unmodified 2′-deoxynucleotides in *S*-type conformations.[8] Also the two stereoisomers of LNA with *xylo*- instead of *ribo*-configuration (i.e., β-D-xylo-LNA and α-L-xylo-LNA corresponding to opposite 3′-configurations as compared to **1** and **2**, Figure 1) have been synthesized and studied. Fully modified β-D-xylo-LNA oligothymidylate sequences demonstrated an affinity for DNA and RNA that is increased as compared to unmodified oligodeoxynucleotides but somewhat decreased as compared to LNA.[6,9] Studies of these four LNA stereoisomers in the "mirror-image world" by mixing the sequences with β-L-configured DNA and RNA demonstrated the features of β-L-LNA, α-D-LNA, β-L-xylo-LNA, and α-D-xylo-LNA.[6] Among these, α-D-LNA has also been synthetically realized,[10] and both α-D-LNA and β-L-LNA form parallel duplexes with complementary RNA of increased thermal stability[6,10] as compared to the well-known parallel-stranded duplex formed between α-D-*ribo*-configured ODNs (α-DNA) and complementary DNA and RNA.[11]

The intriguing hybridization properties of the series of LNA and LNA stereoisomers are based on the locked [2.2.1]bicyclic structure and the resulting inflexible *N*-type conformation.[12] However, natural nucleosides exist in an equilibrium between *N*- and *S*-type conformations with the *E*-type conformation as the transition state conformation.[13] Therefore, also bicyclic nucleosides locked in *E*- or *S*-type conformations are interesting and intensively studied.[2] The [3.2.0]bicyclic nucleoside **3** with an β-D-*arabino* configuration is conformationally locked in the *E*-type conformation and demonstrated in mixmers with 2′-deoxynucleotides and as fully modified sequences somewhat increased hybridization to complementary DNA and RNA.[14] Also its α-anomer (i.e., α-D-*arabino* configuration) has been studied demonstrating the formation of stable parallel duplexes with RNA complementing the properties of α-D-LNA.[15] Many studies toward the synthesis of a perfect locked *S*-type mimic have been performed over the years by us and others,[16−20] but the most obvious solution to the problem, with no unfavorable steric demand in the duplex core, seems to be the [4.3.0]bicyclic 2′-deoxynucleoside **4** with a four-atom 3′,4′-connection and an additional six-membered ring forcing the 2′-deoxyribose moiety into a locked or at least very restricted *S*-type conformation.[18−20] This nucleoside and corresponding ODNs thereof have been only very recently synthesized, and the hybridization was only briefly reported to display a decrease in melting temperature of a DNA:DNA duplex by 3 °C for one modification.[18] The two 2′-*O*-methyl analogues **5** and **6** (with β-D-*ribo*- and β-D-*arabino*-configuration, respectively) have also been studied,[19,20] but whereas the incorporation of **5** synthetically failed, **6** led to significantly decreased hybridization properties, most probably due to an unfavorable steric influence of the 2′-*O*-methyl group.[19] The synthesis of **5** and **6** has been accomplished through a long convergent strategy starting from diacetone-α-D-glucose with oxidation and a stereoselective Grignard reaction as the first key step and with the stereoselectivity controlled by the 1,2-di-*O*-isopropylidine group.[19] Nevertheless, a high number of functional group transformations including nucleobase coupling and protection/deprotections were necessary, giving a synthesis of **5** and **6** in 19 and 21 steps, respectively.[18] The synthesis of **4** by a similar strategy would demand a final 2′-deoxygenation. However, the preparation of **4** was finally accomplished through a linear 17-step synthesis from thymidine.[18]

In the present study, we decided to investigate the locked *S*-type conformation of the [4.3.0]bicyclic skeleton of **4** in combination with other stereoisomers. With the remarkable

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(12) The *N*-type conformation is defined as the conformation with the 3′-carbon puckering to the same side as the 5′-carbon. Therefore, we define **1**, **2**, and **8** as *N*-type mimics, whereas **4**−**7** are defined as *S*-type mimics.

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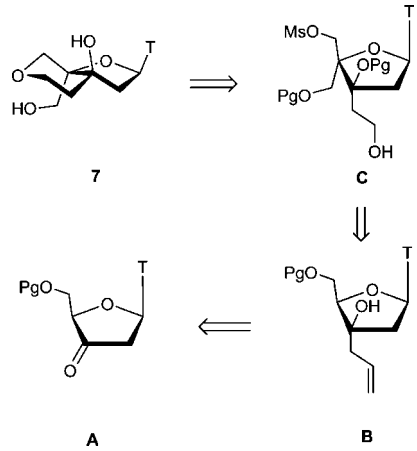


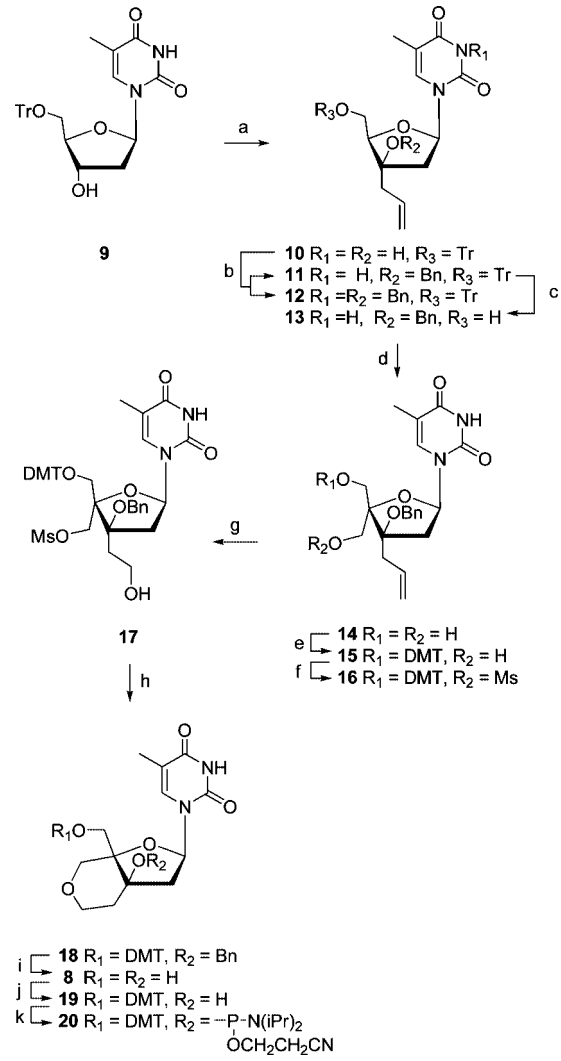
FIGURE 2. Retrosynthesis of compound **7**. T = thymin-1-yl. Pg = protecting group.

properties of α-L-LNA, **2**, in mind, the corresponding α-L-*ribo*-configured *S*-type mimic **7** was our primary goal. Hence, mixmers of **7** with standard 2′-deoxynucleotides might form improved hybridization properties toward DNA and RNA complements and/or toward double-stranded DNA in the formations of triplexes, whereas fully modified sequences might be even more interesting. In the mirror-image world (meaning with L-DNA and L-RNA complements), this bicyclic nucleoside would give immediate information on the α-D-configured analogue and thereby conclude also the study on the scope of parallel duplex formation.[10,11,15,17] The synthesis is envisioned to be much simpler than the synthesis of **4** due to the opposite 3′-configuration (see retrosynthesis in Figure 2). Thus, the reaction of Grignard and organolithium reagents with 5′-*O*-protected 3′-ketonucleosides **A** has been reported to give the *xylo*-configured products with a high stereoselectivity due to the steric influence from the nucleobase.[21,22] Hereby, a 3′-allylcompound **B** should be easily accessible, and subsequent standard 5′-oxidation and aldol condensation followed by double bond cleavage should give **C** and ring-closure the target α-L-*ribo*- configured bicyclic nucleoside **7**. As a secondary goal, also the *β*-D-*xylo*-configured **8** (Figure 1) should be achievable from the same strategy using the 4′-epimer of **C**.

Results and Discussion

Chemical Synthesis of Bicyclic Nucleosides. As the first step in the planned linear synthesis, thymidine was converted to its well-known 5′-tritylated derivative **9** (Scheme 1). Oxidation using PCC and subsequent Grignard reaction with allylmagnesium bromide was accomplished with some difficulties due to the sensitivity of the intermediate ketone to undergo a *β*-elimination of the nucleobase. However, a cerium-assisted Grignard reaction[22] afforded the *β*-D-*xylo*-configured 3′-*C*-allyl nucleoside derivative **10** in a reasonable 41% yield over the two steps. The benzyl group was chosen as a permanent protecting group for the tertiary alcohol. However, benzylation performed at room temperature or with slight cooling afforded the monobenzylated product **11** as well as the dibenzylated **12**. The latter can even be obtained in a high yield with a large excess of benzylbromide (see Supporting Information). However, this dibenzylation was prevented by lowering the reaction temperature further, and the reaction was carried out from −78 °C to room temperature, yielding **11** in 80%.[23] Detritylation of **11** by treatment in refluxing 80% aqueous

SCHEME 1. Preparation of *β*-D-*xylo*-Configured 2′-Deoxynucleoside 8[a]



[a] Reagents and conditions: (a) (i) pyridinium dichromate, CH_2Cl_2, (ii) AllylMgBr, $CeCl_3 \cdot 7H_2O$, THF, −78°C, 41%; (b) NaH, BnBr, THF, −78°C to rt, 80% **11**, 10% **12**; (c) (i) 80% aq AcOH, 90°C, (ii) NaOMe, MeOH, 75%; (d) (i) Dess-Martin periodinane, CH_2Cl_2 or $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, (ii) HCHO, NaOH, 57% or 60%; (e) DMT-Cl, pyridine, 59%; (f) Ms-Cl, CH_2Cl_2, 2,6-lutidine, 82%; (g) OsO_4−$NaIO_4$, then $NaBH_4$, aq THF, 49%; (h) NaH, DMF, 68%; (i) $Pd(OH)_2$/C, EtOH, 86%; (j) DMT-Cl, pyridine, mw 80°C, 93%; (k) $NC(CH_2)_2OP(Cl)N(iPr)_2$, $EtN(iPr)_2$, CH_2Cl_2, 79%. Bn = benzyl, DMT = 4,4′-dimethoxytrityl, Ms = methanesulfunyl.

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acetic acid gave the target 5′-hydroxy compound **13** as well as the corresponding 5-acetylated derivative, wherefore the mixture was treated with sodium methoxide to give **13** as the only product in 75% yield. Oxidation using Dess-Martin periodinane and a subsequent standard aldol condensation followed by Cannizzarro reaction afforded the 4′-*C*-hydroxymethyl nucleoside **14** in 57% yield. On a slightly smaller scale, this oxidation was also accomplished on compound **13** using Swern oxidation conditions, yielding after the aldol/Cannizzarro reaction **14** in 60% yield. Regioselective differentiation between the two primary alcohols in different analogues of **14** has been accomplished before. Nucleosides with *ribo*-configuration have been applied,[24−26] including 3′-*C*-substituted analogues,[18] and also *xylo*-configured nucleosides have been applied.[27] In all cases, the 4′-hydroxymethyl group has been selectively reacted over the 5′-hydroxyl group. The regioselectivity has been deduced to steric hindrance from the nucleobase. Among others, the 4,4′-dimethoxytrityl (DMT) group has been applied,[18,25,27] and therefore, compound **14** was treated with DMT-Cl in pyridine at room temperature to give **15** in 59% yield. No other products were isolated. However, the stereochemistry of C-4′ was not proved at this stage and, in fact, was opposite of what was predicted. Mesylation of **15** gave easily **16** in 82%, and oxidative cleavage of the allyl group and subsequent reduction of the aldehyde was achieved with OsO_4−$NaIO_4$ and $NaBH_4$ to give **17** in 49% yield. The ring closure was accomplished with a treatment of NaH in DMF to give the bicyclic compound **18** in 68% yield. Different reaction conditions to give the selective debenzylation and an intact trityl ether was attempted including the use of ammonium formate, which has been used before to solve a similar problem in the synthesis of α-L-LNA.[9,27] Nevertheless, the best method proved to be a hydrogenation with palladium hydroxide over carbon to give the fully deprotected target nucleoside **8** in 86% yield. The NMR spectra of this compound did not prove the stereochemistry of the bicyclic nucleoside. For instance, the two $^3J_{H1'H2'}$ coupling constants of 2.1 and 8.1 Hz were in accordance with both **7** and **8** expecting a 3′-*endo*/2′-*exo* conformation in both cases. However, the compound was crystallized from methanol, and the single-crystal X-ray structure (Figure 3) revealed that the stereochemistry of the C-4′-position was opposite to that of the expected compound and that the synthetic route resulted in the 2′-deoxynucleoside **8** with β-D-*xylo*-configuration and not the targeted 2′-deoxynucleoside **7** with α-L-*ribo*-configuration.

This result proved that the relative reactivity for the two primary alcohols in **14** were opposite the expected and that the regioselective protection strategy had to be changed. Therefore, mesylation was carried out first using mesylchloride, affording compound **21** as well the dimesylate **22** in 44% and 33% yield, respectively (Scheme 2). Later, compound **22** was reconverted into **21** in 25% yield (or 37% based on the recovery of starting material) by nucleophilic substitution using potassium acetate and 18-crown-6 and subsequent hydrolysis. The position of the mesyl group was determined directly by single-crystal X-ray

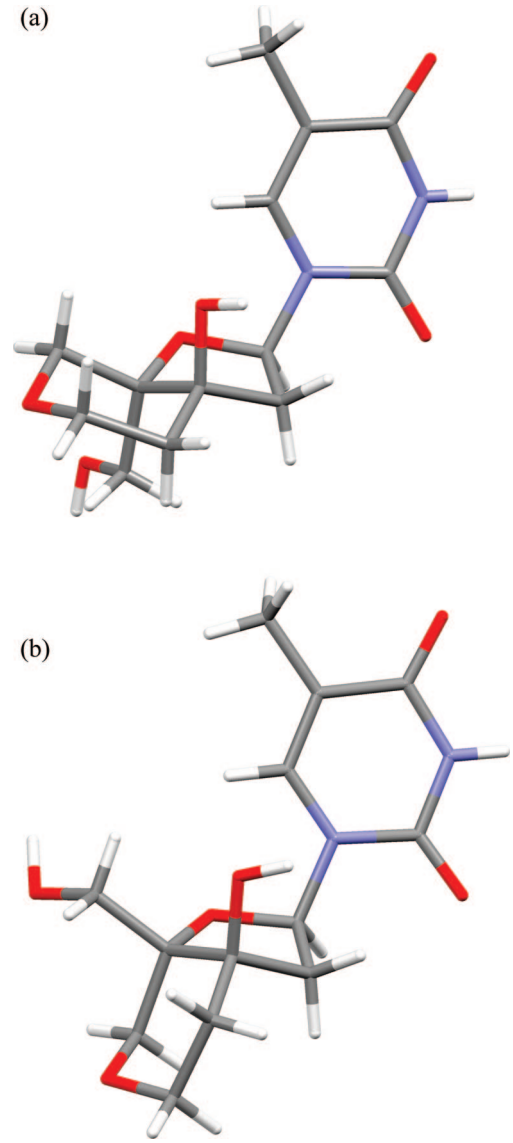

FIGURE 3. X-ray crystal structures of (a) **7** and (b) **8**.

analysis of compound **21**, which was crystalized from CH_2Cl_2 (see Supporting Information). To improve the regioselective reaction by considering steric effect of the 5′-hydroxyl group, activation with the tosyl group as an alternative to the mesyl group was applied. Unfortunately, tosylation by the treatment of **14** with tosylchloride in CH_2Cl_2 in the presence of 2,6-lutidine was very slow and resulted in only 26% yield of the desired compound **23** (or 86% based on the recovery of 70% starting material). The 4′-hydroxymethyl group of the two 5′-sulfonic esters **21** and **23** was blocked with the DMT residue to give **24** and **25** in 75% and 81% yield, respectively. Oxidative cleavage of the allyl group by OsO_4−$NaIO_4$ and subsequent reduction of the aldehyde with $NaBH_4$ was achieved to give compounds **26** and **27** in 48% and 50% yield, respectively. The ring closure was accomplished on both compounds using similar condition as described for **17** (NaH in DMF) to give the bicyclic compound **28** in a 95% yield in both cases. As in the deprotection of **18**, similar attempts were made for a chemoselective debenzylation without detritylation, but hydrogenolysis with catalytic amount of palladium hydroxide over carbon for 10 h at room temperature resulted only in cleavage of the 5′-DMT ether to give **29** still containing the benzyl group. The

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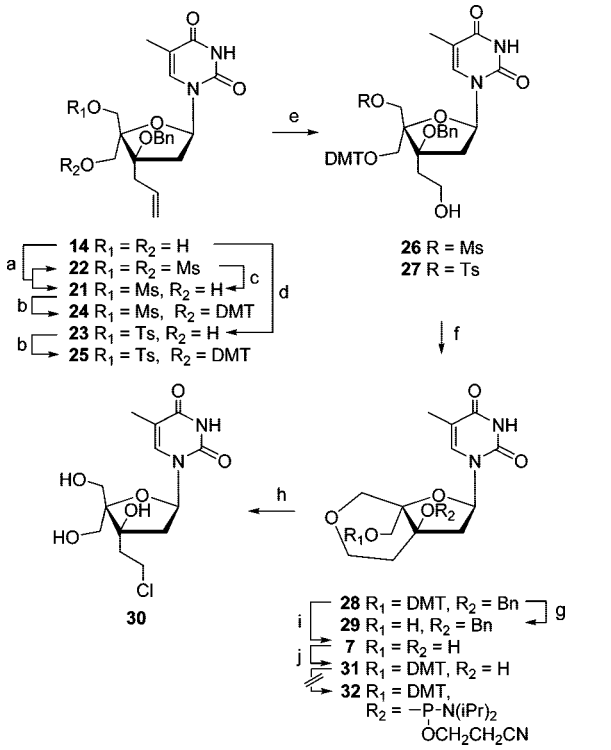
SCHEME 2. Preparation of α-L-*ribo*-Configurated 2′-Deoxynucleoside 7[a]



[a] Reagents and conditions: (a) MsCl, CH_2Cl_2, 2,6-lutidine, 44% **21** + 33% **22**; (b) DMT-Cl, pyridine, 75% **24**, 81% **25**; (c) 18-crown-6, KOAc, CH_2Cl_2, 100°C, 25%; (d) TsCl, CH_2Cl_2, 2,6-lutidine, 26%; (e) OsO_4−$NaIO_4$, $NaBH_4$, aq THF, 48% **26**, 50% **27**; (f) NaH, DMF, 95% from **26**, 95% from **27**; (g) $Pd(OH)_2$/C, EtOH, 89%; (h) BCl_3, CH_2Cl_2, 50%; (i) $Pd(OH)_2$/C, EtOH, 55%; (j) DMT-Cl, pyridine, 97%. Ts = *p*-toluenesulfunyl.

bicyclic structure and the position of the benzyl group was proven by single-crystal X-ray analysis of the compound (see Supporting Information). The debenzylation was therefore attempted using a Lewis acid mediated reaction with BCl_3, but both deprotections and a ring opening of the constrained six-membered ring took place to give compound **30** in 50% yield. Therefore, slightly harsher hydrogenolysis conditions were applied for the debenzylation of **28**. A large excess of palladium hydroxide over carbon was used, and hydrogen gas was passed through the reaction mixture for 5 days to give a fully deprotected target nucleoside **7** in 55% yield. Some depyrimidination was also detected. The fully deprotected target nucleoside **7** was successfully crystallized (as a hydrate) from a solution in methanol for the determination of stereochemistry, and the expected structure was confirmed by single-crystal X-ray analysis (Figure 3). Remarkably, the two $^3J_{H1'H2'}$ coupling constants were found from the ^{1}H NMR spectra to be exactly the same 2.1 and 8.1 Hz for **7** as for compound **8**, indicating exactly the same 3′-*endo* puckering defined as *S*- and *N*-type conformations, respectively.[12]

Synthesis and Evaluation of Oligonucleotides. For the preparation of oligonucleotides by standard solid-phase chemistry using the phosphoramidite approach, the two bicyclic nucleosides **7** and **8** had to be converted into the 5′-*O*-DMT-protected 3′-*O*-phosphoramidites. As shown above, the 5′-DMT group was cleaved during hydrogenolysis in the preparation of both compounds, wherefore a selective retritylation was necessary. This was accomplished in both cases using standard conditions affording selective protection of the primary alcohols to give **19** (Scheme 1) and **31** (Scheme 2) in 93% and 97% yield, respectively. Phosphitylation of compound **19** using standard conditions was successful, giving the phosphoramidite **20** in 79% yield. On the other hand, similar phosphitylation to give the target phosphoramidite **32** from **31** was most unfortunately not successful at all. A wide range of conditions were attempted including 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphoramidite as an alternative phosphitylation reagent with tetrazole or 4,5-dicyanoimidazole as an activator. The reason for the unsuccesful phosphitylation might be found in a significant steric hindrance of the tertiary alcohol of **7**. Thus, a similar phosphitylation of compound **5** has also been reported unsuccessful, whereas the isomer **6** was easily reacted.[19] The pseudoequatorially positioned methylgroup on the α-face of the ring is most probably sterically hindering the 3′-hydroxyl group of **5**. In the case of **7**, the steric problem might be the nucleobase in proximity to the 3′-hydroxy group in a 1,3-diaxial orientation. The reason why **8** is more reactive than **7** might be found in the less constrained bicyclic structure allowing some flexibility and compensation for this steric hindrance.

The phosphoramidite **20** was incorporated into 9-mer ODN sequences with either one or three modifications (Table 1). The same 9-mer sequence as employed in the first study of LNA[3] and other nucleic acid analogues[7,9,26,28] was employed for easy comparison. Coupling of **20** proceeded in high yields, and the composition of the modified oligonucleotides was verified by MALDI MS. The hybridization of the modified ODNs toward complementary DNA and RNA sequences was studied by thermal denaturation experiments, and the melting temperatures of the formed duplexes were determined and compared with the unmodified duplexes (Table 1). These experiments show that a single incorporation of the bicyclic β-D-*xylo*-configured 2′-deoxynucleoside **8** led to decreased affinity for both DNA and RNA, whereas no stable duplexes could be detected in the case of three modifications.

These results demonstrate clearly that the unnatural *xylo*-configuration of **8** is not compatible with natural unmodified 2′-deoxynucleotides in a mixmer sequence concerning the formation of stable duplexes, although the destabilizing effect is somewhat less pronounced for a DNA:RNA duplex than for the DNA:DNA duplex. In the same mixmer sequences, the unrestricted 2′-deoxy-*xylo*-DNA thymine monomer has been found to give only slightly smaller decreases in melting temperature ($\Delta T_m = -6$ in DNA:DNA and −1 °C in DNA:RNA).[28] The β-D-*xylo*-configured LNA-stereoisomer has also been found to be incompatible with 2′-deoxynucleotides in mixmers, as large decreases in melting temperature were observed.[9,28] On the other hand, stable duplexes were formed between fully modified *xylo*-LNA oligothymidylates and complementary DNA and RNA.[9,28] The *xylo*-configured analogue **8** is clearly not as strongly conformationally restricted as the *xylo*-LNA monomer (or as **7** or the other bicyclic analogues shown in Figure 1) due to the *syn*-fused bicyclic system. The large hydrophobic ring might contribute significantly to the large decrease in duplex stability. In the end, the α-L-*ribo*-configuration has shown more intriguing properties than the β-D-*xylo*-configuration in the locked *N*-type conformation of α-L-LNA, **2**, in both fully modified and mixmer contexts.[6,7] Therefore, the failed preparation of the phosphoramidite of the α-L-*ribo*-configured bicyclic target nucleoside **7** with its locked *S*-type

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TABLE 1. Thermal Stability Data of Modified Duplexes

		T_m (ΔT_m), °C[b]	
	ODN sequences[a]	complementary DNA 5′-dGCATATCAC-3′	complementary RNA 5′-rGCAUAUCAC-3′
33	5′-dGTGATATGC-3′	29.0	26.5
34	5′-dGTGA**X**ATGC-3′	21.0 (−8.0)	23.5 (−3.0)
35	5′-dG**X**GA**X**A**X**GC-3′	<10.0 (<−6.0)	<10.0 (<−5.5)

[a] Oligodeoxynucleotide sequences with **X** = **8** (incorporation of **20**). [b] Melting temperatures obtained from the maxima of the first derivatives of the melting curves (A_{260} vs temperature) recorded in a buffer containing 5 mM Na_2HPO_4, 10 mM NaH_2PO_4, 100 mM NaCl, 0.1 mM EDTA, pH 7.0 using 1.0 μM concentrations of each strand. Values in brackets show the changes in T_m values per modification compared with the reference strand.

conformation is, of course, most unfortunate. However, the synthesis of the nucleoside monomer **7** was in fact very efficient, and work on alternative ways for its introduction into oligonucleotides is in progress.

Conclusion

The two bicyclic 2′-deoxynucleosides **7** and **8** with α-L-*ribo*- and β-D-*xylo*-configurations and restricted *S*- and *N*-type conformations, respectively, were each prepared as planned from the retrosynthetic analysis in only 12 synthetic steps. This makes their preparation much more straightforward than the corresponding synthesis of the β-D-*ribo*-configured stereoisomer **4**. Only the β-D-*xylo*-configured *N*-type mimic **8** has been incorporated into oligodeoxynucleotides leading to decreased hybridization affinity for complementary DNA and RNA.

Experimental Section

Assignments of NMR spectra follow standard nucleoside style, i.e., the carbon atom next to a nucleobase is assigned as C-1′ and so on. C-1″, C-2″, and C-3″ designate the carbon atoms attached to the 3′-C branch, and C-5″ designates the carbon atom attached to the C-4′ branch.

Preparation of 1-*N*-(3′-*C*-Allyl-5′-*O*-trityl-2′-deoxy-β-D-xylofuranosyl)thymine (10). A slurry of 3Å molecular sieves powder (5.25 g) and pyridiniumdichromate (3.73 g, 9.92 mmol) in anhydrous CH_2Cl_2 (50 mL) was stirred. A solution of nucleoside **9** (4.0 g, 8.26 mmol) in anhydrous CH_2Cl_2 (20 mL) was added. The dark brown mixture was stirred for 5 h and then filtered through 3Å molecular sieves powder (deposited as a slurry with anhydrous CH_2Cl_2) on a sintered glass filter. The plug was washed with anhydrous CH_2Cl_2 (100 mL), and the combined filtrate was concentrated under reduced pressure to 10 mL. To the brown mixture was added anhydrous EtOAc (600 mL) causing some of the chromium salts to precipitate. The mixture was filtered through 3Å moleculer sieves powder (deposited as a slurry with anhydrous EtOAc) on a sintered glass filter. The residue was washed with anhydrous EtOAc (150 mL), and the combined filtrate was concentrated under reduced pressure. $CeCl_3 \cdot 7H_2O$ (18.0 g, 48.31 mmol) was dried at 190 °C under vacuum for 16 h and then cooled to room temperature under nitrogen atmosphere. Anhydrous THF (150 mL) was added, and the slurry was stirred at −78 °C. AllylMgBr in anhydrous Et_2O (1M, 50 mL, 50.0 mmol) was added dropwise, and the slurry was stirred for 1 h at −78 °C. The crude nucleoside (3.91 g, 8.12 mmol) was dissolved in anhydrous THF (50 mL), cooled to −78 °C, and canulated slowly to the slurry. The reaction mixture was stirred for 16 h at −78 °C. Glacial acetic acid (10 mL) was added, and the reaction mixture was partitioned between EtOAc (600 mL) and water (200 mL). The organic phase was washed with water (2 × 200 mL) and brine (3 × 150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−5%) in dichloromethane) affording **10** (1.78 g, 41%) as a white solid. R_f 0.60 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.97 (bs, 1H, NH), 7.86 (s, 1H, H-6), 7.47−7.20 (m, 15H, Ar), 6.16 (dd, 1H, J = 2.7, 8.1 Hz, H-1′), 5.72 (m, 1H, H-2″), 5.08−4.99 (m, 2H, H-3″), 3.79 (t, 1H, J = 3.6 Hz, H-4′), 3.70−3.61 (m, 2H, H-5′, 3′-OH), 3.48 (dd, 1H, J = 3.6, 10.8 Hz, H-5′), 2.45 (dd, 1H, J = 8.1, 14.7 Hz, H-2′), 2.33−2.08 (m, 3H, H-1″, H-2′), 1.82 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2 (C-4), 150.7 (C-2), 143.1 (C-6), 137.4 (Ar), 132.5 (C-2″), 128.8, 128.3, 127.6 (Ar), 119.6 (C-3″), 110.3 (C-5), 88.0 (CAr_3), 79.0 (C-3′), 84.3, 84.0 (C-4′, C-1′), 62.1 (C-5′), 45.0 (C-2′), 42.6 (C-1″), 12.6 (CH_3); HR-MALDI MS *m*/*z* (547.2180 [M + Na]$^+$, $C_{32}H_{32}N_2O_5$ − Na$^+$ calcd 547.2203).

Preparation of 1-*N*-(3′-*C*-Allyl-3′-*O*-benzyl-5′-*O*-trityl-2′-deoxy-β-D-xylofuranosyl)thymine (11) and 1-*N*-(3′-*C*-Allyl-3′-*O*-benzyl-5′-*O*-trityl-2′-deoxy-β-D-xylofuranosyl)-3-*N*-benzylthymine (12). A solution of the allyl derivative **10** (2.5 g, 4.77 mmol) in anhydrous THF (200 mL) was stirred at −78 °C. Sodium hydride (60% in oil w/w, 860 mg, 21.50 mmol) was added, and after 1 h of stirring, benzyl bromide (2 mL, 16.84 mmol) was added dropwise. The reaction mixture was brought to room temperature in 10 h and stirred over 5 days at room temperature. The reaction was quenched by slow addition of a mixture of H_2O and a saturated aqueous solution of $NaHCO_3$ (1:1, v/v, 50 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phase was washed with H_2O (3 × 20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−2%) in dichloromethane) affording **11** (2.33 g, 80%) as a white foam as well as **12** (334 mg, 10%). Compound **11**: R_f 0.70 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (bs, 1H, NH), 7.56−7.14 (m, 19H, H-6, Ar), 6.94−6.91 (m, 2H, Ar), 6.09 (t, 1H, J = 5.1 Hz, H-1′), 5.71 (m, 1H, H-2″), 5.17−5.04 (m, 2H, H-3″), 4.38, 4.05 (AB, 2H, J = 11.1 Hz, OCH_2Ar), 4.28 (t, 1H, J = 6.0 Hz, H-4′), 3.54−3.47 (m, 2H, H-5′), 2.62−2.50 (m, 2H, H-1″), 2.44−2.40 (m, 2H, H-2′), 1.27 (d, 3H, J = 0.9 Hz, CH_3); ^{13}C NMR (75 MHz, CDCl3) δ 163.7 (C-4), 150.3 (C-2), 143.8, 137.4, 136.4 (C-6, Ar), 132.2 (C-2″), 128.8, 128.5, 128.0, 127.7, 127.2, 126.9 (Ar), 119.9 (C-3″), 109.6 (C-5), 87.3, 83.5 (CAr_3, C-3′), 86.3 (C-4′), 84.9 (C-1′), 64.4 (OCH_2Ar), 62.8 (C-5′), 39.6 (C-2′), 37.3 (C-1″), 12.0 (CH_3); HR-MALDI MS *m*/*z* (637.2670 [M + Na]$^+$, $C_{39}H_{38}N_2O_5$ − Na$^+$ calcd 637.2673). Compound **12**: R_f 0.80 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49−7.12 (m, 24H, H-6, Ar), 6.82 (d, 2H, J = 7.2 Hz, Ar), 6.08 (dd, 1H, J = 3.6, 5.7 Hz, H-1′), 5.70 (m, 1H, H-2″), 5.14−4.98 (m, 4H, H-3″, NCH_2Ar), 4.32, 3.96 (AB, 2H, J = 11.1 Hz, OCH_2Ar), 4.27 (t, 1H, J = 5.4 Hz, H-4′), 3.53−3.47 (m, 2H, H-5′), 2.58−2.52 (m, 2H, H-1″), 2.42−2.39 (m, 2H, H-2′), 1.30 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4 (C-4), 151.0 (C-2), 143.8, 137.4, 137.2, 134.4 (C-6, Ar), 132.2 (C-2″), 129.2, 128.8, 128.4, 128.4, 127.9, 127.6, 127.2, 126.8 (Ar), 119.8 (C-3″), 108.9 (C-5), 87.2, 83.4 (CAr_3, C-3′), 86.3 (C-4′), 85.6 (C-1′), 64.4 (OCH_2Ar), 62.8 (C-5′), 44.2 (NCH_2Ar), 39.6 (C-2′), 37.3 (C-1″), 12.8 (CH_3); HR-MALDI MS *m*/*z* (727.3113 [M + Na]$^+$, $C_{46}H_{44}N_2O_5$ − Na$^+$ calcd 727.3142).

Preparation of 1-*N*-(3′-*C*-Allyl-3′-*O*-benzyl-2′-deoxy-β-D-xylofuranosyl)thymine (13). A solution of compound **11** (7.86 g, 12.80 mmol) in 80% aqueous acetic acid (150 mL) was stirred at 90 °C for 6 h. The solution was concentrated under reduced pressure, and

the residue was coevaporated with ethanol (2 × 30 mL) and toluene (20 mL). The residue was redissolved in anhydrous methanol (100 mL) and added sodium methoxide (692 mg, 12.81 mmol), and the mixture was stirred for 17 h at room temperature and then neutralized with dilute aqueous hydrochloric acid. The mixture was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−5%) in dichloromethane) to give compound **13** as a white foam (3.57 g, 75%). R_f 0.30 (CH_2Cl_2/CH_3OH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (bs, 1H, NH), 7.70 (s, 1H, H-6), 7.35−7.16 (m, 5H, Ar), 6.10 (dd, 1H, J = 3.6, 6.9 Hz, H-1′), 5.84 (m, 1H, H-2″), 5.27−5.21 (m, 2H, H-3″), 4.55, 4.18 (AB, 2H, J = 10.5 Hz, OCH_2Ar), 4.12−3.98 (m, 3H, H-4′, H-5′), 2.79 (dd, 1H, J = 6.6, 15.0 Hz, H-1″), 2.59−2.41 (m, 3H, H-1″, H-2′), 1.60 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (C-4), 150.5 (C-2), 136.8 (Ar), 136.2 (C-6), 128.9, 128.3, 127.6 (Ar), 131.6 (C-2″), 120.3 (C-3″), 110.2 (C-5), 86.3 (C-4′), 85.1 (C-3′), 84.2 (C-1′), 65.5 (OCH_2Ar), 61.8 (C-5′), 40.5 (C-2′), 38.1 (C-1″), 12.3 (CH_3); HR-MALDI MS m/z (395.1562 [M + Na]$^+$, $C_{20}H_{24}N_2O_5$ − Na^+ calcd 395.1577).

Preparation of 1-*N*-(3′-*C*-Allyl-3′-*O*-benzyl-4′-*C*-hydroxymethyl-2′-deoxy-β-D-xylofuranosyl)thymine (14). Compound **13** (3.55 g, 9.54 mmol) was coevaporated with anhydrous pyridine (2 × 10 mL) and toluene (2 × 10 mL) and then redissolved in anhydrous CH_2Cl_2 (50 mL). Dess-Martin periodinane (8.09 g, 19.08 mmol) was added, and the white and nonclear reaction mixture was stirred for 5 h at room temperature. The reaction mixture was filtered through celite (deposited as slurry with CH_2Cl_2 on a glass filter). The plug was washed with CH_2Cl_2 (100 mL), and the resulting solution was washed with a mixture of a saturated aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$ (1:1, v/v, 80 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude aldehyde (quantative) was dissolved in dioxane (50 mL), an aqueous solution of formaldehyde (37%, 2.09 mL, 25.77 mmol) was added, and then an aqueous solution of sodium hydroxide (2 M, 4.77 mL, 9.54 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 14 h. The mixture was cooled to 0 °C, sodium borohydride (363 mg, 9.55 mmol) was added slowly, and the mixture was stirred at room temperature for 3 h. Then, a mixture of pyridine and glacial acetic acid (4:1, v/v, 50 mL) was added, and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (methanol (0−5%) in dichloromethane) affording **14** (2.19 g, 57%) as a white solid. R_f 0.30 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (300 MHz, CD_3OD) δ 7.65 (d, 1H, J = 1.2 Hz, H-6), 7.35−7.23 (m, 5H, Ar), 6.19 (d, 1H, J = 5.7 Hz, H-1′), 6.10−5.96 (m, 1H, H-2″), 5.30−5.19 (m, 2H, H-3″), 4.58, 4.28 (AB, 2H, J = 10.5 Hz), 4.14, 3.86 (AB, 2H, J = 12.6 Hz), 3.95, 3.79 (AB, 2H, J = 12.3 Hz), 2.98 (dd, 1H, J = 5.7, 15.9 Hz, H-1″), 2.78−2.59 (m, 3H, H-1″, H-2′), 1.40 (d, 3H, J = 1.2 Hz, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 166.5 (C-4), 152.3 (C-2), 139.1 (Ar), 138.6 (C-6), 134.5 (C-2″), 129.5, 128.7 (Ar), 118.9 (C-3″), 110.0 (C-5), 94.7, 87.0 (C-4′, C-3′), 86.5 (C-1′), 64.7, 64.1, 63.5 (OCH_2Ar, C-5″, C-5′), 42.7 (C-2′), 36.3 (C-1″), 12.2 (CH_3); HR-MALDI MS m/z (425.16.81 [M + Na]$^+$, $C_{21}H_{26}N_2O_6$ − Na^+ calcd 425.1683).

Preparation of 1-*N*-[3′-*C*-Allyl-3′-*O*-benzyl-5′-*O*-(4,4′-dimethoxytrityl)-4′-*C*-hydroxymethyl-2′-deoxy-β-D-xylofuranosyl]thymine (15). Compound **14** (2.16 g, 5.37 mmol) was coevaporated with anhydrous pyridine (2 × 5 mL) and toluene (2 × 5 mL) and then redissolved in anhydrous pyridine (15 mL). DMTCl (2.28 g, 6.73 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. Water (2 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−3%) in dichloromethane containing 0.5% pyridine) affording **15** (2.25 g, 59%) as a white foam. R_f 0.60 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (bs, 1H, NH), 7.45−7.15 (m, 13H, H-6, Ar), 6.92 (dd, 2H, J = 3.6, 6.9 Hz, Ar), 6.80 (dd, 4H, J = 0.9, 8.7 Hz, Ar), 6.25 (d, 1H, J = 6.3 Hz, H-1′), 5.65−5.51 (m, 1H, H-3″), 5.09 (d, 1H, J = 5.4 Hz, H-2″), 4.91 (d, 1H, J = 16.8 Hz, H-3″), 4.35, 4.01 (AB, 2H, J = 10.8 Hz), 4.19 (dd, 1H, J = 4.5, 11.7 Hz, H-5″), 3.90 (dd, 1H, J = 5.1, 11.7 Hz, H-5″), 3.77−3.73 (m, 7H), 3.44 (d, 1H, J = 11.1 Hz), 2.78 (dd, 1H, J = 6.3, 16.2 Hz, H-1″), 2.67−2.35 (m, 3H, H-1″, H-2′), 1.18 (d, 3H, J = 0.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (C-4), 158.7 (Ar), 150.5 (C-2), 144.5, 137.2, 136.6, 135.7, 135.6 (C-6, Ar), 132.3 (C-2″), 130.1, 130.1, 128.4, 128.2, 128.0, 127.7, 127.0, 126.9, 113.3 (Ar), 118.9 (C-3″), 109.5 (C-5), 93.2, 86.8, 85.7 (CAr_3, C-4′, C-3′), 85.3 (C-1′), 65.1, 63.4 (OCH_2Ar, C-5′), 64.3 (C-5″), 55.3 (OCH_3), 40.9 (C-2′), 35.1 (C-1″), 11.9 (CH_3); HR-MALDI MS m/z (727.2992 [M + Na]$^+$, $C_{42}H_{44}N_2O_8$ − Na^+ calcd 727.2990).

Preparation of 1-*N*-[3′-*C*-Allyl-3′-*O*-benzyl-5′-*O*-(4,4′-dimethoxytrityl)-4′-*C*-methanesulfonyloxymethyl-2′-deoxy-β-D-xylofuranosyl]thymine (16). To a stirred solution of compound **15** (2.21 g, 3.14 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C were added 2,6-lutidine (2.5 mL, 21.56 mmol) and methanesulfonyl chloride (0.98 mL, 12.60 mmol), and the mixture was stirred at room temperature for 10 h. The reaction mixture was cooled to 0 °C, and water (3 mL) was added followed by a saturated aqueous solution of $NaHCO_3$ (5 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−2%) in dichloromethane containing 0.5% pyridine) affording **16** (2.01 g, 82%) as a white solid. R_f 0.50 (CH_2Cl_2/MeOH 19:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (bs, 1H, NH), 7.42−7.10 (m, 13H, H-6, Ar), 6.95−6.92 (m, 2H, Ar), 6.80 (d, 4H, J = 8.7 Hz, Ar), 6.29 (d, 1H, J = 6.6 Hz, H-1′), 5.52 (m, 1H, H-2″), 5.19 (d, 1H, J = 10.2 Hz, H-3″), 4.98 (d, 2H, J = 16.8 Hz, H-3″), 4.79, 4.50 (AB, 2H, J = 11.1 Hz), 4.36, 4.05 (AB, 2H, J = 10.8 Hz), 3.79−3.76 (m, 7H), 3.40 (d, 1H, J = 10.8 Hz), 3.11 (s, 3H, CH_3SO_2), 2.85 (dd, 1H, J = 4.5, 15.6 Hz, H-1″), 2.62−2.44 (m, 3H, H-1″, H-2′), 1.16 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C-4), 158.7 (Ar), 150.4 (C-2), 144.3, 136.7, 136.2, 135.4, 135.3, 131.3 (C-6, Ar), 131.3 (C-2″), 130.1, 128.6, 128.2, 128.0, 127.9, 127.1, 126.9, 113.3 (Ar), 119.8 (C-3″), 109.9 (C-5), 91.6, 86.9, 85.6, 85.5 (CAr_3, C-4′, C-3′, C-1′), 70.3, 64.5, 63.6, (OCH_2Ar, C-5″, C-5′), 55.3 (OCH_3), 41.1 (C-2′), 37.5 (CH_3SO_2), 35.1 (C-1″), 11.9 (CH_3); HR-MALDI MS m/z (805.2765 [M + Na]$^+$, $C_{43}H_{46}N_2O_{10}S$ − Na^+ calcd 805.2751).

Preparation of 1-*N*-[3′-*O*-Benzyl-5′-*O*-(4,4′-dimethoxytrityl)-3′-*C*-(2-hydroxyethyl)-4′-*C*-methanesulfonyloxymethyl-2′-deoxy-β-D-xylofuranosyl]thymine (17). To a solution of nucleoside **16** (1.94 g, 2.48 mmol) in a mixture of THF (6 mL) and water (6 mL) were added sodium periodate (1.59 g, 7.46 mmol) and a 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (203 μL, 0.02 mmol). The reaction was stirred at room temperature for 22 h and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined extract was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was redissolved in a mixture of THF (7.5 mL) and water (7.5 mL), and sodium borohydride (283 mg, 7.45 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h, water (2 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−2%) in dichloromethane containing 0.5% pyridine) affording **17** (960 mg, 49%) as a white foam. R_f 0.40 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (bs, 1H, NH), 7.45−7.11 (m, 13H, H-6, Ar), 6.93−6.90 (m, 2H, Ar), 6.80 (d, 4H, J = 8.4 Hz, Ar), 6.23 (d, 1H, J = 6.0 Hz, H-1′), 4.76, 4.71 (AB, 2H, J = 11.1 Hz), 4.24, 4.01 (AB, 2H, J = 11.1 Hz), 3.82−3.75 (m, 7H), 3.61−3.52 (m, 2H), 3.08 (s, 3H, CH_3SO_2), 2.67−2.48 (m, 2H, H-2′), 2.25 (m, 1H,

H-2″), 2.05 (m, 1H, H-2″), 1.74−1.68 (m, 2H, H-1″), 1.19 (d, 3H, $J = 0.9$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C-4), 158.7 (Ar), 150.4 (C-2), 144.3, 136.7, 136.1, 135.4, 135.3, 130.2, 130.2, 128.6, 128.3, 128.0, 127.9, 127.2, 126.8, 113.3 (C-6, Ar), 109.8 (C-5), 91.8, 87.0, 85.6 (CAr_3, C-4′, C-3′), 85.3 (C-1′), 70.6, 63.9, 63.6, 57.5 (OCH_2Ar, C-5″, C-5′, C-2″), 55.3 (OCH_3), 41.4 (C-2′), 37.5 (CH_3SO_2), 33.4 (C-1″), 11.9 (CH_3); HR-MALDI MS *m/z* (809.2715 $[M + Na]^+$, $C_{42}H_{46}N_2O_{11}S - Na^+$ calcd 809.2699).

Preparation of (1*R*,6*R*,8*R*)-6-Benzyloxy-1-(4,4′-dimethoxytrityloxymethyl)-8-(thymin-1-yl)-3,9-dioxabicyclo[4.3.0]nonane (18). Compound **17** (600 mg, 0.76 mmol) was dissolved in anhydrous DMF (1.5 mL), and a suspension of sodium hydride (60% in oil, w/w, 92 mg, 2.30 mmol) in anhydrous DMF (0.5 mL) was added dropwise at 0 °C. The reaction was stirred at room temperature for 3 h and then quenched with water (1 mL). The mixture was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (2 × 2 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate (0−70%) in petroleum ether containing 0.5% pyridine) affording **18** (358 mg, 68%) as a white foam. R_f 0.50 (petroleum ether/EtOAc 1:3); ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (bs, 1H, NH), 7.50−7.09 (m, 13H, H-6, Ar), 6.90 (dd, 2H, $J = 3.3$, 7.2 Hz, Ar), 6.84−6.78 (m, 4H, Ar), 6.15 (d, 1H, $J = 6.0$ Hz, H-1′), 4.71, 3.13 (AB, 2H, $J = 12.0$ Hz), 4.29 (d, 1H, $J = 11.1$ Hz), 4.03−3.95 (m, 2H), 3.76 (s, 6H, OCH_3), 3.64, 3.53 (AB, 2H, $J = 11.1$ Hz), 3.43 (m, 1H, H-2″), 2.76 (dd, 1H, $J = 7.5$, 15.6 Hz, H-2′), 2.34 (m, 1H, H-2′), 2.07 (m, 1H, H-1″), 1.81 (ddd, 1H, $J = 5.7$, 12.3, 18.0 Hz, H-1″), 1.21 (d, 3H, $J = 0.9$ Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (C-4), 158.5, (Ar), 150.3 (C-2), 144.9, 137.2, 136.5, 136.0, 136.0, 130.3, 130.3, 128.5, 128.3, 128.4, 127.9, 127.7, 126.9, 113.2 (C-6, Ar), 109.4 (C-5), 86.6, 86.4, 81.7 (CAr_3, C-4′, C-3′), 85.0 (C-1′), 68.5, 63.1, 62.2 (OCH_2Ar, C-5″, C-5′), 65.1 (C-2″), 55.2 (OCH_3), 37.0 (C-2″), 30.4 (C-1″), 11.9 (CH_3); HR-MALDI MS *m/z* (713.2846 $[M + Na]^+$, $C_{41}H_{42}N_2O_8 - Na^+$ calcd 713.2833).

Preparation of (1*S*,6*R*,8*R*)-6-Hydroxy-1-hydroxymethyl-8-(thymin-1-yl)-3,9-dioxabicyclo[4.3.0]nonane (8). To a stirred solution of nucleoside **18** (340 mg, 0.49 mmol) in ethanol (5 mL) was added 20% palladium hydroxide over carbon (690 mg, 0.99 mmol). The mixture was degassed several times with argon and placed under a hydrogen atmosphere. The reaction mixture was stirred at room temperature for 7 h and then filtered through celite. The filter was washed with ethanol (3 × 10 mL), and the combined filterate was concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−8%) in dichloromethane) affording nucleoside **8** as a white foam (126 mg, 86%). R_f 0.10 (CH_2Cl_2/CH_3OH 9:1); ^1H NMR (300 MHz, CD_3OD) δ 8.07 (d, 1H, $J = 1.2$ Hz, H-6), 6.13 (dd, 1H, $J = 2.4$, 8.1 Hz, H-1′), 4.04 (d, 2H, $J = 12.3$ Hz), 3.90−3.80 (m, 2H), 3.51 (ddd, 1H, $J = 3.0$, 11.7, 14.7 Hz, H-2″), 3.11 (d, 1H, $J = 12.3$ Hz), 3.01 (dd, 1H, $J = 8.1$, 15.0 Hz, H-2′), 2.06 (dd, 1H, $J = 2.4$, 15.0 Hz, H-2′), 1.99−1.94 (m, 2H, H-1″), 1.88 (d, 3H, $J = 1.2$ Hz, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 166.5 (C-4), 152.4 (C-2), 139.4 (C-6), 110.4 (C-5), 86.7, 77.3 (C-4′, C-3′), 85.5 (C-1′), 68.6, 62.3 (C-5″, C-5′), 66.2 (C-2″), 44.2 (C-2′), 35.7 (C-1″), 12.5 (CH_3); HR-MALDI MS *m/z* (321.1052 $[M + Na]^+$, $C_{13}H_{18}N_2O_6 - Na^+$ calcd 321.1057).

Preparation of (1*R*,6*R*,8*R*)-1-(4,4′-Dimethoxytrityloxymethyl)-1-hydroxy-8-(thymin-1-yl)-3,9-dioxabicyclo[4.3.0]nonane (19). The bicyclic nucleoside **8** (106 mg, 0.36 mmol) was dissolved in anhydrous pyridine (1.0 mL) and DMTCl (301 mg, 0.89 mmol) was added in one portion. The mixture was heated in a microwave vial at 80 °C for 30 min. The reaction was quenched by the addition of methanol (0.5 mL), and the mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 2 mL) and brine (1 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−3%) in dichloromethane containing 0.5% pyridine) affording **19** (199 mg, 93%) as a white foam. R_f 0.60 (CH_2Cl_2/CH_3OH 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H, H-6), 7.45−7.16 (m, 9H, Ar), 6.85 (d, 4H, $J = 9.0$ Hz, Ar), 6.24 (dd, 1H, $J = 2.1$, 8.1 Hz, H-1′), 4.78 (bs, 1H, 3′-OH), 3.87 (dd, 1H, $J = 5.1$, 12.0 Hz, H-2″), 3.79 (s, 6H, OCH_3), 3.71−3.60 (m, 3H), 3.36 (m, 1H, H-2″), 3.10 (d, 1H, $J = 12.3$ Hz), 2.89 (dd, 1H, $J = 8.1$, 14.7 Hz, H-2′), 2.14 (dd, 1H, $J = 2.1$, 14.7 Hz, H-2′), 1.96 (m, 1H, H-1″), 1.81 (s, 3H, CH_3), 1.73 (m, 1H, H-1″); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0 (C-4), 158.9 (Ar), 150.8 (C-2), 144.0, 137.3, 135.0, 134.7, 130.1, 130.0, 128.3, 128.0, 127.3, 113.5 (C-6, Ar), 110.5 (C-5), 88.0, 84.5, 77.7 (CAr_3, C-4′, C-3′), 83.6 (C-1′), 70.5, 64.7 (C-5″, C-5′), 65.7 (C-2″), 55.3 (OCH_3), 42.8 (C-2′), 35.0 (C-1″), 12.6 (CH_3); HR-MALDI MS *m/z* (623.2359 $[M + Na]^+$, $C_{34}H_{36}N_2O_8 - Na^+$ calcd 623.2364).

Preparation of (1*R*,6*R*,8*R*)-6-(2-Cyanoethoxy(diisopropylamino)phosphinoxy)-1-(4,4′-dimethoxytrityloxymethyl)-8-(thymin-1-yl)-3,9-dioxabicyclo[4.3.0]nonane (20). The DMT-protected nucleoside **19** (63 mg, 0.10 mmol) was coevaporated with anhydrous CH_2Cl_2 (2 × 3 mL) and dissolved in anhydrous CH_2Cl_2 (0.7 mL). *N*,*N*-Diisopropylethylamine (0.11 mL, 0.63 mmol) followed by 2-cyanoethyl-*N*,*N*-diisopropylphosphoramidochloridite (94 μL, 0.42 mmol) were added, and the mixture was stirred at room temperature for 10 h. The reaction was quenched with methanol (0.5 mL) and the mixture was dissolved in ethyl acetate (2 mL), washed with a saturated aqueous solution of $NaHCO_3$ (2 × 2 mL) and brine (1 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−2%) in dichloromethane containing 0.5% pyridine) affording **20** as a white foam (66 mg, 79%). R_f 0.70 (CH_2Cl_2/MeOH 9:1), ^{31}P NMR (75 MHz, $CDCl_3$) δ 144.9, 143.0; HR-MALDI MS *m/z* (823.3474 $[M + Na]^+$, $C_{43}H_{53}N_4O_9P - Na^+$ calcd 823.3442).

Preparation of 1-*N*-(3′-*C*-Allyl-3′-*O*-benzyl-4′-*C*-hydroxymethyl-5′-*O*-methanesulfonyl-2′-deoxy-β-D-xylofuranosyl)thymine (21) and 1-*N*-(3′-*C*-Allyl-3′-*O*-benzyl-4′-*C*-methanesulfonyloxymethyl-5′-*O*-methanesulfonyl-2′-deoxy-β-D-xylofuranosyl)thymine (22). Method A: To a stirred solution of 14 (1.05 g, 2.61 mmol) in anhydrous CH_2Cl_2 (40 mL) at 0 °C were added 2,6-lutidine (345 μL, 2.98 mmol) and methanesulfonyl chloride (230 μL, 2.96 mmol), and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (acetone (10−30%) in dichloromethane) affording compound **21** as white foam (554 mg, 44%) as well as the dimesylated compound **22** (493 mg, 33%). Method B: To a solution of **22** (600 mg, 1.04 mmol) in dioxane (20 mL) were added potassium acetate (490 mg, 5.0 mmol) and 18-crown-6 (528 mg, 2.0 mmol). The reaction mixture was stirred at 105 °C for 4 days and then cooled. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was redissolved in a saturated methanolic solution of NH_3 (30 mL), and the solution was stirred for 20 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (acetone (10−30%) in dichloromethane) affording compound **21** as a white foam (125 mg, 25%) as well as 30% of the starting material **22**. Compound **21**: R_f 0.22 (CH_2Cl_2/CH_3OH 19:1); ^1H NMR (300 MHz, DMSO-d_6) δ 11.22 (s, 1H, NH), 7.44 (d, 1H, $J = 0.9$ Hz, H-6), 7.36−7.21 (m, 5H, Ar), 6.17 (t, 1H, $J = 4.5$ Hz, H-1′), 5.93 (m, 1H, H-2″), 5.40 (t, 1H, $J = 5.1$ Hz, 5″-OH), 5.26−5.11 (m, 2H, H-3″), 4.63, 4.41 (AB, 2H, $J = 11.1$ Hz), 4.48, 4.29 (AB, 2H, $J = 11.1$ Hz), 3.73−3.58 (m, 2H, H-5″), 3.17 (s, 3H, CH_3SO_2), 2.94 (dd, $J = 6.3$, 15.7 Hz, 1H, H-1″), 2.66−2.59 (m, 3H, H-1″, H-2′), 1.35 (d, 3H, $J = 0.9$ Hz, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.6 (C-4), 151.2 (C-2), 138.6 (Ar), 136.7 (C-6), 134.2, 129.2, 128.3, 128.2 (Ar, C-2″), 119.7 (C-3″), 109.5 (C-5), 91.3, 85.0, (C-3′, C-4′), 86.7 (C- 1′), 70.5, 63.9 (OCH_2Ar, C-5′), 62.4 (C-5″), 41.1 (C-2′), 38.0 (CH_3SO_2), 35.6 C-1″), 12.7

(CH_3); HR-ESI MS *m/z* 503.1472 ([M + Na]$^+$, $C_{22}H_{28}N_2O_8S$ − Na^+ calcd 503.1459). Compound **22**. R_f 0.40 (CH_2Cl_2/CH_3OH 19:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (s, 1H, NH), 7.42 (d, 1H, J = 1.2 Hz, H-6), 7.37−7.16 (m, 5H, Ar), 6.22 (dd, 1H, J = 2.1, 7.2 Hz, H-1′), 5.84 (m, 1H, H-2″), 5.40−5.30 (m, 2H, H-3″), 4.90 (d, 1H, J = 11.1 Hz), 4.54−4.39 (m, 4H), 4.19 (d, 1H, J = 10.5 Hz) 3.14 (s, 3H, CH_3SO_2), 3.07 (s, 3H, CH_3SO_2), 3.01 (m, 1H, H-1″), 2.74−2.51 (m, 3H, H-1″, H-2′), 1.52 (d, J = 1.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C-4), 150.4 (C-2), 136.1, 135.6 (Ar, C-6), 130.9 (C-2″), 129.0, 128.5, 127.6 (Ar), 120.6 (C-3″), 110.7 (C-5), 89.5, 85.6 (C-3′, C-4′), 86.0 (C- 1′), 68.4, 68.0, 64.6 (C-5′, C-5″, OCH_2Ar), 41.0 (C-2′), 38.0, 37.8 (2 × CH_3SO_2), 35.1 (C-1″), 12.1 (CH_3); HR-ESI MS *m/z* (581.1225 [M + Na]$^+$, $C_{23}H_{30}N_2O_{10}S_2$ − Na^+ calcd 581.1234).

Preparation of 1-*N*-[3′-*C*-Allyl-3′-*O*-benzyl-4′-*C*-(4,4′-dimethoxytrityloxymethyl)-5′-*O*-methanesulfonyl-2′-deoxy-β-D-xylofuranosyl]thymine (24). To a stirred solution of **21** (250 mg, 0.52 mmol) in anhydrous pyridine (6 mL) was added DMT-Cl (300 mg, 0.88 mmol). The reaction was stirred for 24 h at room temperature, CH_2Cl_2 (30 mL) was added, and the mixture was washed with a saturated aqueous solution of $NaHCO_3$ (30 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (acetone (0−10%) in dichloromethane) affording **24** as a white foam (305 mg, 75%). R_f 0.57 (CH_2Cl_2/acetone 19:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (s, 1H, NH), 7.61−7.21 (m, 15H, H-6, Ar), 7.16−7.12 (m, 4H, Ar), 6.48 (d, J = 6.6 Hz, 1H, H-1′), 5.60 (m, 1H, H-2″), 5.02 (d, 1H, J = 12.0 Hz), 4.92 (d, 1H, J = 10.5 Hz, H-3″), 4.46−4.42 (m, 2H, H-3″, H-5′), 4.21−4.14 (m, 2H), 3.79 (s, 6H, OCH_3), 3.69, 3.08 (AB, 2H, J = 10.8 Hz), 3.04−2.94 (m, 4H, H-2′, CH_3SO_2), 2.80−2.63 (m, 2H, H-2′, H-1″), 2.23 (dd, 1H, J = 9.6, 15.9 Hz, H-1″), 1.56 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (C-4), 158.8 (Ar), 150.4 (C-2), 143.9, 136.4 135.5, 135.0 (C-6, Ar), 131.4 (C-2″), 130.2, 130.0, 128.8, 128.2, 128.2, 127.6, 127.3 (Ar), 119.8 (C-3″), 113.5 (Ar), 110.1 (C-5), 91.7 (C-3′), 88.0 (CAr_3), 86.4 (C-1′), 86.1 (C-4′), 70.2, 64.2, 63.7 (OCH_2Ar, C-5″, C-5′), 55.4 (OCH_3), 41.6 (C-2′), 38.4 (CH_3SO_2), 34.7 (C-1″), 12.0 (CH_3); HR-ESI MS *m/z* (805.2752 [M + Na]$^+$, $C_{43}H_{46}N_2O_{10}S$ − Na^+ calcd 805.2765).

Preparation of 1-*N*-[3′-*O*-Benzyl-4′-*C*-(4,4′-dimethoxytrityloxymethyl)-3′-*C*-(2-hydroxyethyl)-5′-*O*-methanesulfonyl-2′-deoxy-β-D-xylofuranosyl]thymine (26). To a solution of compound **24** (1.15 g, 1.47 mmol) in a mixture of THF (15 mL) and water (15 mL) were added sodium periodate (820 mg, 3.83 mmol) and a 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (81.0 μL, 0.008 mmol). The reaction mixture was stirred at room temperature for 24 h. Water (30 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was redissolved in a mixture of THF (10 mL) and water (10 mL) and cooled to 0 °C, and sodium borohydride (380 mg, 10.0 mmol) was added. The mixture was stirred for 2 h at room temperature, and water (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic phase was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−2%) in dichloromethane) affording compound **26** as a white foam (560 mg, 48%). R_f 0.49 (CH_2Cl_2/CH_3OH 19:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (s, 1H, NH), 7.59−6.85 (m, 19H, H-6, Ar), 6.33 (d, 1H, J = 6.3 Hz, H-1′), 4.99, 4.52 (AB, 2H, J = 12.0 Hz), 4.29, 4.07 (AB, 2H, J = 10.5 Hz), 3.79 (s, 6H, OCH_3), 3.58−3.52 (m, 3H), 3.29 (d, 1H, J = 10.5 Hz), 2.95 (s, 3H, CH_3SO_2), 2.86−2.63 (m, 2H, H-2′), 2.12 (m, 1H, H-1″), 1.76 (m, 1H, H-1″), 1.56 (d, 3H, J = 1.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8 (C-4), 158.8 (Ar), 150.4 (C-2), 143.9, 136.4, 136.1, 135.2, 135.0, 130.2, 130.1, 128.8, 128.2, 127.4, 127.3, 113.5 (C-6, Ar), 110.2 (C-5), 91.7 (C-3′), 86.1 (C- 1′), 87.9, 85.9 (CAr_3, C- 4′), 69.8, 64.2, 64.0 (OCH_2Ar, C-5″, C-5′), 57.6 (C-2″), 55.4 (OCH_3), 41.8 (C-2′), 38.2 (CH_3SO_2), 33.1 (C-1″), 12.1 (CH_3); HR-ESI MS *m/z* (809.2715 [M + Na]$^+$, $C_{42}H_{46}N_2O_{11}S$ − Na^+ calcd 809.2729).

Preparation of (1*S*,6*R*,8*R*)-6-*O*-Benzyl-1-(4,4′-dimethoxytrityloxymethyl)-8-(thymin-1-yl)-3,9-dioxabicyclo[4.3.0]nonane (28). Method 1: To a stirred suspension of sodium hydride (60% in oil, w/w, 20 mg, 0.5 mmol) in anhydrous DMF (1 mL) at 0 °C was slowly added a solution of **26** (115 mg, 0.15 mmol) in anhydrous DMF (1 mL). The reaction mixture was stirred at room temperature for 4 h. The reaction was quenched with water (15 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was coevaporated with xylene and purified by column chromatography (methanol (0−3%) in dichloromethane) affording compound **28** as a white foam (96 mg, 95%). Method 2: The same procedure using compound **27** (200 mg, 0.23 mmol), sodium hydride (60% in oil, w/w, 40 mg, 1.0 mmol), and DMF (4 mL) afforded compound **28** (152 mg, 95%). R_f 0.66 (CH_2Cl_2/CH_3OH 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H, NH), 7.41−7.12 (m, 15H, H-6, Ar), 6.77 (d, 4H, J = 8.1 Hz, Ar), 6.01 (d, 1H, J = 7.2 Hz, H-1′), 4.32 (d, 1H, J = 9.5 Hz), 4.24 (d, 1H, J = 10.5 Hz), 3.96−3.92 (m, 2H), 3.72 (s, 6H, OCH_3), 3.63−3.55 (m, 3H), 3.17 (d, 1H, J = 10.2 Hz, H-2″), 2.46 (m, 1H, H-2′), 2.29 (d, 1H, J = 14.4 Hz, H-2′), 2.00 (d, 1H, J = 14.0 Hz, H-1″), 1.49 (m, 1H, H-1″), 1.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9 (C-4), 158.6 (Ar), 150.4 (C-2), 144.6, 137.1, 136.8, 135.9, 135.7, 130.2, 130.1, 128.8, 128.2, 128.1, 128.1, 127.6, 127.0, 113.3 (C-6, Ar), 109.1 (C-5), 87.0, 84.6, 79.9 (C−Ar_3, C-3′, C-4′), 86.0 (C-1′), 65.9, 63.0, 61.7 (OCH_2Ar, C-5″, C-5′), 64.9 (C-2″), 55.4 (OCH_3), 38.5 (C-2′), 28.2 (C-1″), 12.0 (CH_3); HR-ESI MS *m/z* (713.2833 [M + Na]$^+$, $C_{41}H_{42}N_2O_8$ − Na^+ calcd 713.2816).

Preparation of (1*R*,6*R*,8*R*)-6-Hydroxy-1-hydroxymethyl-8-(thymin-1-yl)-3,9-dioxabicyclo[4.3.0]nonane (7). To a stirred solution of **28** (120 mg, 0.17 mmol) in ethanol (3 mL) was added 20% palladium hydroxide over carbon (243 mg, 0.35 mmol). This mixture was bubbled with hydrogen for 5 days under stirring. Methanol (10 mL) was added, the mixture was filtered through celite, and the filter was washed with methanol (5 × 5 mL). The combined filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (methanol (0−10%) in dichloromethane) affording nucleoside **7** (28 mg, 55%) as a white solid. R_f 0.18 (CH_2Cl_2/CH_3OH 9:1): ^{1}H NMR (300 MHz, CD_3OD) δ 8.03 (s, 1H, H-6), 6.15 (dd, 1H, J = 2.1, 8.1 Hz, H-1′), 4.09 (d, 1H, J = 9.3 Hz), 3.98−3.73 (m, 4H), 3.54 (d, 1H, J = 12.0 Hz), 2.65 (m, 1H, H-2′), 2.02 (m, 1H, H-2′), 1.90−1.76 (m, 5H, H-1″, CH_3); ^{13}C NMR (75 MHz, CD_3OD) δ 166.5 (C-4), 152.5 (C-2), 140.0 (C-6), 109.9 (C-5), 86.4 (C-4′), 85.0 (C-1′), 74.6 (C-3′), 65.5, 63.1, 62.4 (C-5′, C-2″, C-5″), 44.8 (C-2′), 34.5 (C-1″), 12.5 (CH_3); HR-MALDI MS *m/z* (321.1065 [M + Na]$^+$, $C_{13}H_{18}N_2O_6$ − Na^+ calcd 321.1057).

Preparation of (1*S*,6*R*,8*R*)-1-(4,4′-Dimethoxytrityloxymethyl)-6-hydroxy-8-(thymin-1-yl)-3,9-dioxabicyclo[4.3.0]nonane (31). Compound **7** (85 mg, 0.28 mmol) was dissolved in anhydrous pyridine (3.0 mL), and DMT-Cl (120 mg, 0.35 mmol) was added in one portion. The mixture was stirred at room temperature for 24 h. Dichloromethane (20 mL) was added, and the mixture was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 20 mL), and the combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (methanol (0−3%) in dichloromethane containing 0.5% pyridine) affording the DMT-protected derivative **31** (166 mg, 97%) as a white foam. R_f 0.30 (CH_2Cl_2/CH_3OH 95:5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (bs, 1H, NH), 7.46−7.18 (m, 10H, H-6, Ar), 6.83 (d, 4H, J = 9.0 Hz, Ar), 5.50 (dd, 1H, J = 1.8, 7.8 Hz, H-1′), 4.17, 3.99 (AB, 2H, J = 9.6 Hz), 3.89

(m, 1H), 3.78 (s, 6H, OCH_3), 3.75 (s, 1H, 3′-OH), 3.65−3.60 (m, 2H), 3.08 (d, 1H, $J = 9.9$ Hz, H-2″), 2.45 (dd, 1H, $J = 8.1$, 14.0 Hz, H-2′), 2.18 (d, 1H, $J = 14.0$ Hz, H-2′), 1.88 (s, 3H, CH_3), 1.70−1.56 (m, 2H, H-1″); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4 (C-4), 158.6 (Ar), 151.2 (C-2), 144.5, 138.8, 136.2, 136.0, 130.1, 130.0, 128.4, 128.0, 127.0, 113.3 (C-6, Ar), 108.4 (C-5), 86.8, 85.3, 74.2 (CAr_3, C-4′, C-3′), 86.3 (C-1′), 66.4, 62.2 (C-5″, C-5′), 64.2 (C-2″), 55.3 (OCH_3), 43.3 (C-2′), 33.8 (C-1″), 12.6 (CH_3); HR-MALDI MS *m/z* (623.2364 $[M + Na]^+$, $C_{34}H_{36}N_2O_8 - Na^+$ calcd 623.2348).

X-ray Crystallography. Single-crystal X-ray analysis of **8**, **21**, and **29** was performed at 180(2) K, and **7**·H_2O was analyzed at room temperature. In all cases, H atoms bound to C and N atoms were placed in geometrically idealized positions and allowed to ride on their parent atoms during subsequent refinement. H atoms of the OH groups were located in difference Fourier maps and refined without restraint with isotropic displacement parameters. In **21**, the presence of the S atoms permitted determination of the absolute structure via refinement of the Flack parameter (refined value 0.00(5)). In **7**·H_2O, **8**, and **29**, the lack of significant anomalous scattering meant that the absolute structure could not be determined reliably, and Friedel pairs were merged as equivalent data prior to the final cycles of refinement. Crystallographic data for **7**·H_2O, **8**, **21**, and **29** have been deposited at the Cambridge Crystallographic Data Centre (deposition numbers 698429−698432).

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Supporting Information Available: General introduction to the experimental section and the experimental details for the compounds **23**, **25**, **27**, **29**, and **30** as well as the compounds describing the synthetic steps from **12** toward a bicyclic nucleoside;[23] crystallographic data for **7**·H_2O, **8**, **21**, and **29** in CIF format; experimental details for the preparation and evaluation of oligonucleotides and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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