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Screening the Structural Space of Bicyclo-DNA: Synthesis and Thermal Melting Properties of bc^{4,3}-DNA

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In attempts to screen the structural and functional properties of bicyclo-DNA, in which the ribose C(3′) and C(5′) centers are integrated into an additional five-membered carbocyclic ring ([3.3.0]-series) we have now synthesized and investigated a ring enlarged analogue in which C(5′) and C(3′) are spanned by a six-membered carbocyclic ring ([4.3.0]-series). The synthesis of the corresponding bc^{4,3}-T nucleoside **13** was performed in 12 steps by starting from known allyl furanose **1**. X-ray analysis of its benzyl protected precursor **12** showed the cyclohexane ring to adopt a chair conformation with the O(5′) substituent in an axial position. The furanose part shows clearly S-type sugar pucker. This nucleoside was converted into the corresponding phosphoramidite building block **15** and incorporated into oligodeoxynucleotides by standard phosphoramidite chemistry. The thermal stabilities of oligonucleotides with single or double incorporations of bc^{4,3}-T residues, paired to complementary DNA or RNA, were found to be similar to those of unmodified oligonucleotides (–2.3 to +0.7 °C per modification) and to those with the known bc-T modifications. We also found that mismatch discrimination in the bc^{4,3}-T series was similar to that of the natural series but less discriminative in comparison to the known bc-T series.

Introduction

In vitro and in vivo attenuation of gene expression can be achieved by complementary Watson–Crick base-pairing of antisense oligonucleotides (ASOs) with RNA targets. A wide variety of strategies in the design and synthesis of modified ASOs have been applied in the last 30 years to increase target specificity and affinity and to decrease in vivo toxicity.[1] The concept of conformational restriction[2] has been successfully applied in nucleic acid chemistry and has brought forward a large variety of analogues, such as the bridged nucleic acids (LNA/BNA),[3] the hexitol nucleic acids (HNA),[4] and tricyclo-DNA (tc-DNA),[5] all of which show increased affinity towards complementary RNA without base-pairing properties being compromised. Not only are these advanced analogues expected to replace the phosphorothioates and 2′-modified analogues in therapy,[6] but in some cases they have also proven to increase siRNA efficacy.[7]

Our first-generation, conformationally restricted oligonucleotide analogue [3.3.0]bicyclo-DNA (bc-DNA)[8a,8b] shows no significant improvement in Watson–Crick pairing to RNA relative to that of DNA, probably due to a structural mismatch in the repetitive backbone unit at torsion angle γ [C(4′)–C(5′), Figure 1], which as a consequence of the carbocyclic ring prefers an *ac* [pseudoequatorial O(5′)-substituent] conformation in nucleoside monomers and dimers.[8c,8d]

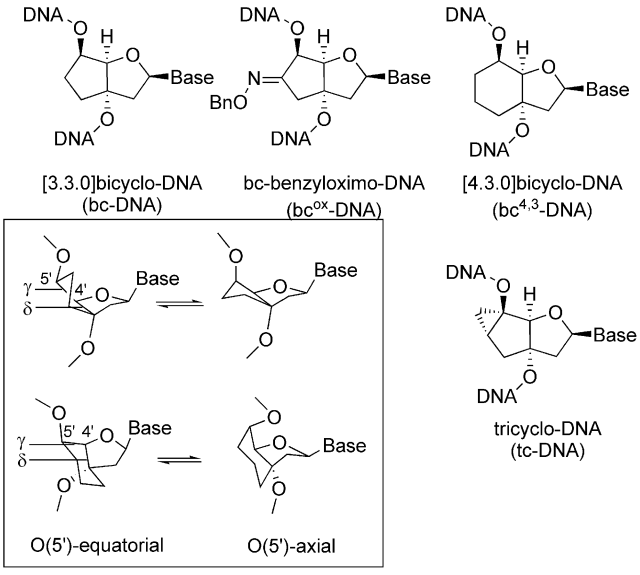

Figure 1. Chemical structures of [3.3.0]bicyclo-DNA (bc-DNA), bc^{ox}-DNA, [4.3.0]bicyclo-DNA, (bc^{4,3}-DNA), and tricyclo-DNA (tc-DNA), as well as conformational features of the carbocyclic rings in the bc[4.3.0]- and [3.3.0]-series (box).

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With the background of establishing a structure–affinity relationship in the bicyclo-DNA family, several analogues, such as bc^{ox}-DNA,[9] are currently under investigation in our laboratory. An interesting candidate in this context is [4.3.0]bicyclo-DNA (bc^{4,3}-DNA, Figure 1). We reasoned that annealing a six-membered instead of a five-membered ring to the furanose unit will have an additional rigidifying effect on the carbocyclic structure, because of the reduced number of different conformational states of a cyclohexane ring relative to those of a cyclopentane ring. Furthermore, the transition from a five- to a six-membered ring is expected to shift specifically the conformational preferences of the backbone torsion angles γ and δ. (Figure 1). A bc^{4,3}-nucleoside precursor with the base thymine was previously synthesized by Nielsen and coworkers.[10a] An alternative synthesis for bc^{4,3}-T was disclosed recently by our laboratory.[11] However, this nucleoside has never been structurally investigated nor inserted into oligonucleotides. Here we report on an alternative synthesis of [4.3.0]bicyclothymidine, its conformational preferences as determined by computer modeling and X-ray crystallography, as well as on the incorporation into oligodeoxyribonucleotides by solid-phase phosphoramidite chemistry and on the base-pairing properties with complementary DNA and RNA.

Results and Discussion

Molecular Modeling

A conformational search of the 5′*O*- and 3′*O*-methylated T-monomer as a model for the nucleoside [no H-bond donor at O(3′,5′)] by molecular modeling with the use of Hyperchem software[12] revealed the lowest-energy conformer with a six-membered ring chair conformation to be that with the O(5′) atom in an equatorial position (28.08 kcal mol^{-1}). This compares to the energy of the other possible chair conformation with the O(5′) atom in the axial position (31.50 kcal mol^{-1}), which is higher in energy by 3.42 kcal mol^{-1} (Figure 2).

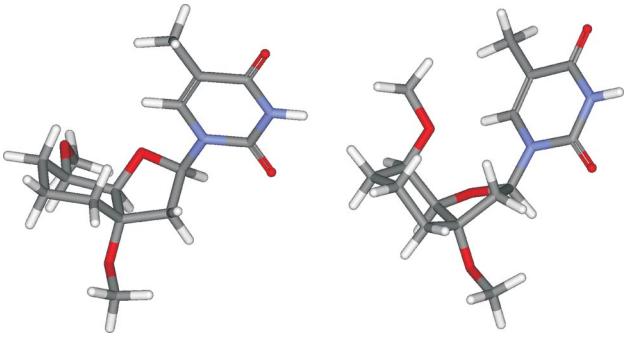


Figure 2. Conformational search. The O(5′) atom in the equatorial (left) and axial (right) orientations. The two structures differ by 3.42 kcal mol^{-1}.

In an energy-minimized structure of a fully modified [4.3.0]bicyclo-DNA oligonucleotide paired to its complementary DNA, the six-membered ring adopts a twist-boat conformation with the O(5′) atom in an pseudoaxial orientation. The furanose puckering is O(4′)-*endo* (Figure 3).

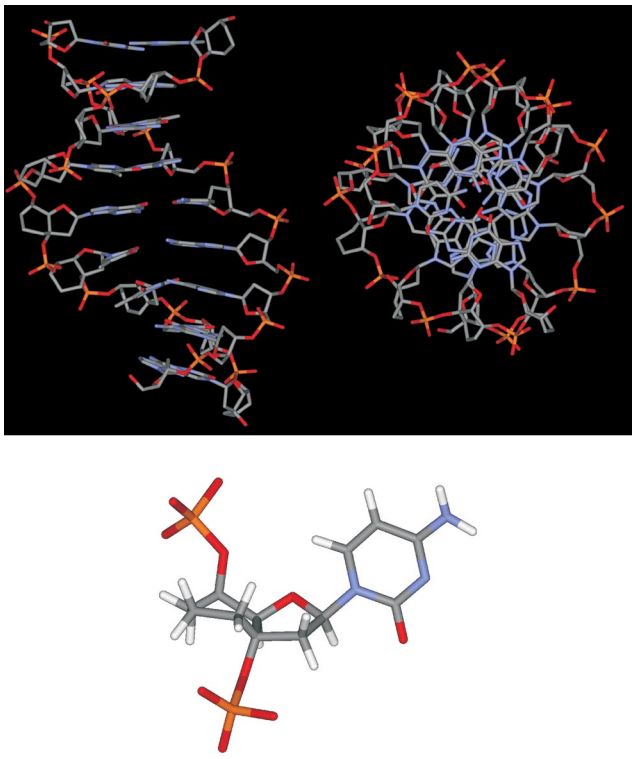
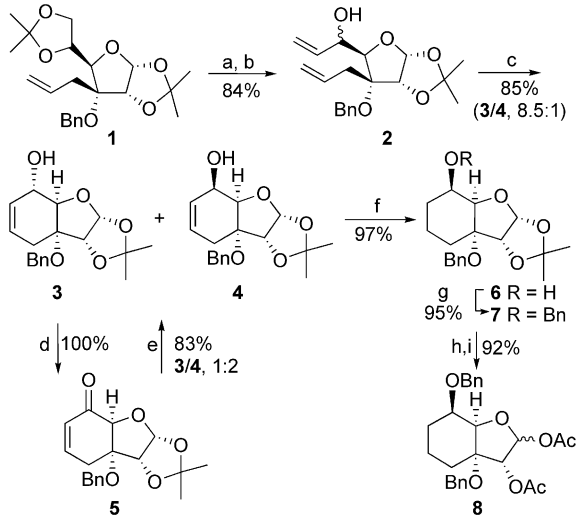


Figure 3. Top: Energy-minimized molecular model of a DNA duplex containing a fully modified [4.3.0]bicyclo-DNA oligonucleotide. Bottom: Structure of an average monomeric unit in the duplex.

Synthesis of the Nucleoside Building Block

The synthesis of phosphoramidite building block **15** started from C(3′)-allylfuranose **1**, which was obtained in three steps from diacetone-D-glucose (Scheme 1)[10e,10f] by following a strategy similar to that described previously by Nielsen et al.[10a–10d] Oxidative and selective cleavage of the exposed glycol was efficiently performed with periodic acid in ethyl acetate to give the corresponding 5′-carboxaldehyde.[13] Subsequent Grignard reaction with vinylmagnesium bromide yielded **2** as a mixture of stereoisomers. Both isomers were smoothly converted into [4.3.0]bicyclo derivatives **3** and **4** (*S*/*R*, 8.5:1) by ring-closing metathesis with the use of Grubb's 2nd generation catalyst (2 mol-%). Undesired 5′*S* isomer **3**, the relative configuration of which was unambiguously assigned by NMR-ROESY spectroscopy, was subsequently oxidized with Dess–Martin periodinane to enone **5**, followed by Luche reduction to give again a mixture of stereoisomers **3** and **4**, however, now in a ratio of 2:1 in favor of desired *R* isomer **4**. After catalytic hydrogenation (→**6**) and benzylation of the OH func-

tion (→**7**), the dioxolane ring was hydrolyzed in boiling acetic acid, followed by acetylation to give sugar building block **8** in excellent yield.

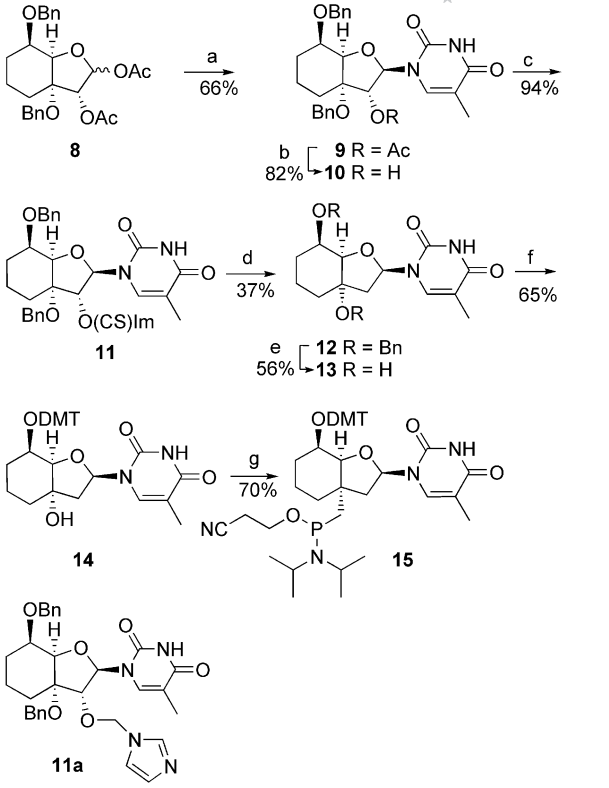


Scheme 1. Synthesis of [4.3.0]bicyclosugar. Reagents and conditions: (a) H_5IO_6 (1.1 equiv.), EtOAc, room temp., 90 min; (b) vinylMgBr (1.8 equiv.), THF, room temp., 16 h; (c) Grubbs' catalyst 2nd generation (2 mol-%), CH_2Cl_2, 40 °C, 3 h (ratio of **3/4**, 8.5:1); (d) Dess–Martin periodinane (1.5 equiv.), CH_2Cl_2, room temp., 4 h; (e) $CeCl_3 \cdot 7H_2O$ (2 equiv.), $NaBH_4$ (2 equiv.), MeOH, 0 °C, 30 min (ratio of **3/4**, 1:2); (f) 20% $Pd(OH)_2/C$, H_2, MeOH, room temp., 3 h; (g) NaH (2 equiv.), DMF, 50 °C, 1 h, then BnBr (2 equiv.), DMF, room temp., 16 h; (h) 80% aq. AcOH, 90 °C, 16 h; (i) Ac_2O, pyridine, room temp., 16 h.

Nucleosidation of **8** with persilylated thymine under Vorbrüggen conditions[14] (Scheme 2) led to nucleoside **9** with high selectivity for the β-anomer (ratio α/β, 1:10) and in good yield. 2′-*O*-Deprotected analogue **10** was obtained by treating **9** with sodium methoxide in methanol.

In preparing for removal of the C(2′)–OH group, the thiocarbonylimidazole substituent was introduced to yield **11** in excellent yield. Deoxygenation under Barton–McCombie conditions[15] gave deoxy analogue **12**, however, only in poor yield (37%). Various conditions were tested to improve the outcome of this reaction (summarized in Table 1). Best yields were found with AIBN as a radical starter and Bu_3SnH (3 equiv.) in toluene (Table 1, Entry 1). Very high concentrations of Bu_3SnH led to complete turnover of the starting material; however, there was a 3:1 preference for starting alcohol **10** over deoxygenated product **12** (Table 1, Entry 2). A change in the solvent to *t*BuOH did not improve the reaction either (Table 1, Entry 3). As an alternative to tin hydride as a hydrogen donor, tris(trimethylsilyl)silane (TTMSS), introduced by Chatgilialoglu[16] was used (Table 1, Entry 4). However, the only product isolated was side product **11a** (Scheme 2), which is known to occur in deoxygenations as a consequence of an alternative radical pathway.[15a,15b,16a,17]

Despite the described problems with the defunctionalization at the C(2′) position, deoxy derivative **12** was obtained in sufficient quantities to continue the synthesis. Deprotection by catalytic hydrogenation gave free monomer



Scheme 2. Synthesis of [4.3.0]bicyclothymidine phosphoramidite. Reagents and conditions: (a) thymine (2 equiv.), BSA (5 equiv.), TMSOTf (1.4 equiv.), CH_3CN, 40 °C, 16 h; (b) NaOMe (2 equiv.), MeOH, room temp., 16 h; (c) 1,1′-thiocarbonyldiimidazol (1.5 equiv.), room temp., DMF, 6 h; (d) AIBN (1 equiv.), Bu_3SnH (3 equiv.), toluene, 80 °C, 4 h; (e) 20% $Pd(OH)_2/C$, cyclohexa-1,4-diene (10 equiv.), H_2, MeOH, room temp., 6 h; (f) DMTOTf (1.5 equiv.), pyridine, room temp., 24 h; (g) CEPCl (3 equiv.), Hünig's base (5 equiv.), CH_3CN, room temp., 2 h.

Table 1. Reagents and conditions for the reduction of **11**.

Entry	Conditions	Products (yield, %)
1	AIBN (1 equiv.), Bu_3SnH (3 equiv.), toluene, 90 °C, 4 h	**12/11/10**, 2:1:1 (79)
2	AIBN (0.8 equiv.), Bu_3SnH (32 equiv.), toluene, 75 °C, 2 h	**12/10**, 1:3 (n.d.)[a]
3	AIBN (0.8 equiv.), Bu_3SnH (3 equiv.), *t*BuOH, 75 °C, 16 h	**12/11/10**, 2:1:1 (n.d.)[a]
4	AIBN (0.1 equiv.), TTMSS[b] (2 equiv.), toluene, 80 °C, 48 h	**11a** (<20)

[a] n.d. = yield not determined. [b] TTMSS = tris(trimethylsilyl)-silane.

13 in 55% yield. As a side reaction, reduction of the base was observed Although different conditions (e.g., different palladium catalysts, high or normal pressure of H_2, addition of cyclohexa-1,4-diene as hydrogen source) were tested, no optimal deprotection scheme was found. Attempts to reoxidize 5,6-dihydrothymine to **13** according to literature procedures[18] were unsuccessful. Despite these difficulties, free monomer **13** was further converted into phosphoramidite building block **15** by dimethoxytritylation (→**14**) and phosphitylation.

X-ray Structure of Nucleoside 12

Crystals of benzyl-protected nucleoside **12** were subjected to X-ray analysis to map the conformational preferences of the bicyclic core structure (Figure 4, see also Supporting Information). Two individual molecules (**12a**,**b**) coexist in the unit cell, which essentially differ in the orientation of the O(3′) benzyl group. There are no intramolecular hydrogen bonds detectable that could influence the local conformation of the sugar ring.

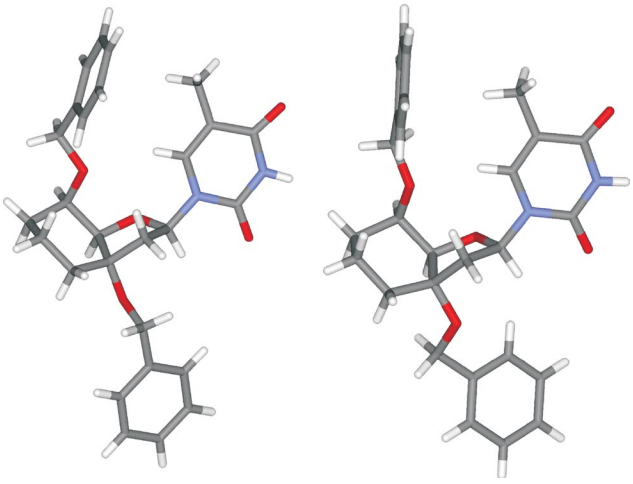


Figure 4. X-ray structure of nucleoside **12a** (left) and **12b** (right). The two independent molecules per asymmetric unit differ mostly in the orientation of the O(3′) benzyl groups.

The furanose ring adopts a C(2′)-*endo* conformation (^{2}E, south-type) and thus gives rise to a pseudorotational phase angle *P* of 174° for **12a** and 166° for **12b** (Table 2).[19] For torsion angle ν_4 [C(3′)–C(4′)–O(4′)–C(1′)][20] the values are –9.1 (for **12a**) and –3.7 (for **12b**), hence showing a quasiplanar alignment of the four atoms. The orientation of the base (torsion angle χ) is, as expected, *anti*.

Table 2. Pseudorotation phase angles and selected nucleoside torsion angles of [4.3.0]bicyclo-DNA nucleoside **12** in relation to bc-nucleosides and natural deoxyribonucleosides in the B conformation.

Nucleoside	*P*[a] [°]	γ [°]	δ [°]	χ [°]
12a	174	70	162	–105
12b	166	71	154	–120
bc-T[b]	128	149	126	–113
bc^{ox}-T[c]	163	88	148	–118
dN[d]	144	57	122	–119

[a] Pseudorotation phase angle. [b] Taken from ref.[8c] [c] Taken from ref.[9] [d] Average deoxynucleotide conformation in B-DNA (ref.[20]).

The carbocyclic ring shows a chair-like conformation with the hydroxy group at C(5′) in an axial position. As a consequence, torsion angle γ is in a *gauche* (+*sc*) orientation as observed in A- and B-DNA. Comparison with the X-ray structure of the parent bc-T shows a shift in the conformation of the furanose ring from the C(1′)-*exo* to the C(2′)-*endo* form and a change in the torsion angle γ from the *anticlinal* to the *gauche* range. These structural properties are comparable to the recently published structure of benzyloximobicyclothymidine (bc^{ox}-T).[9]

There is clearly a discrepancy between the X-ray and energetically preferred modeled structure of **12**. In the X-ray structure, the cyclohexane ring exists in the chair conformation with the O(5′) substituent in an axial position, which by modeling was found to be higher in energy by 3.42 kcal mol^{-1} relative to the alternative chair conformation with the O(5′) substituent in an equatorial position. Interestingly, in the X-ray structure C(5)–H and the methyl group of thymine make close contacts to the π system of the O(5′) benzyl group, reminiscent of π–σ* interactions. Although **12** adopts a conformation in the X-ray structure that is much closer to that of a natural nucleotide in the DNA backbone, it cannot be ruled out that intramolecular or packing forces in **12** are enforcing a higher energy conformer.

Oligonucleotide Synthesis

A series of dodecamers (ON**1**, ON**2**, and ON**4**; Table 3) and a decamer (ON**6**; Table 5) of mixed-base oligonucleotides containing single or double [4.3.0]bc-T mutations were synthesized on a 1 μM or 1.3 μM scale by standard phosphoramidite chemistry. For incorporation of the modified building blocks, the standard coupling step was extended to 12–14 min and the phosphoramidite concentration was increased up to 0.2 M. Coupling efficiencies were generally lower (≈90%) relative to those of [3.3.0]bc-amidites. Crude oligonucleotides were deprotected and detached from the solid support by using standard conditions (conc. NH_3, 55 °C, 16 h). All oligonucleotides were purified by HPLC and their structural composition was analyzed by ESI-MS (for details see the Supporting Information).

T_m Measurements

UV melting curve analysis was performed at 260 nm with a cooling–heating–cooling cycle at a rate of 0.5 °C min^{-1} in standard saline buffer at pH 7.0. All curves within a cycle were superimposable, thus ruling out nonequilibrium states. The experimental T_m data are summarized in Tables 3 and 5.

Table 3. T_m data from UV melting curves (260 nm) of modified dodecamer duplexes with complementary DNA and RNA.

	Oligonucleotide[a]	X	T_m vs. DNA [°C][b]	T_m vs. RNA [°C][b]
ON**1**	d(GGA**X**GTTCTCGA)bc^{4,3}-T		46.1 (–1.4)	47.4 (–2.3)
ON**2**	d(GGATGTTC**X**CGA)bc^{4,3}-T		47.3 (–0.2)	48.9 (–0.8)
ON**3**	d(GGATGTTC**X**CGA) bc-T		49.0 (+1.5)	49.0 (–0.7)
ON**4**	d(GGATG**XX**CTCGA)bc^{4,3}-T		47.0 (–0.3)	51.0 (+0.7)
ON**5**	d(GGATG**XX**CTCGA) bc-T		48.7 (+0.6)	48.2 (–0.7)

[a] T_m of unmodified oligodeoxynucleotide: 47.5 °C (vs. DNA); 49.7 °C (vs. RNA). [b] ΔT_m per modification in parenthesis; *c* = 2 μM in 10 mM NaH_2PO_4, 150 mM NaCl, pH 7.0.

Analysis of the T_m data revealed a slight reduction in the thermal stability of duplexes containing one or two [4.3.0]-bicyclothymidines against DNA and RNA. Duplexes involving ON**1** with the modification in between two purine bases and closer to the 5′-end show the highest degree of destabilization. Duplexes with ON**2** and ON**4** show about the same stability as natural duplexes. A slight stabilizing effect can be seen for the ON**4**/RNA duplex (+0.7 °C/modification), an observation which might indicate that consecutive modifications lead to stabilization of the duplex in comparison to the natural system. Relative to the parent [3.3.0]bicyclo series (ON**3** and ON**5**) there exist only minor variations in the values of T_m. There is a weak tendency for more stable duplexes of bc-T with complementary DNA and for bc^{4,3}-T with complementary RNA.

To determine the relative effect of the modifications on pairing selectivity we measured the T_m data for the singly modified oligonucleotide ON**2** with complementary DNA carrying a mismatched base opposite the modification. For comparison, the sense strands carrying bc-T, bc^{ox}-T, and a natural thymidine were also measured (data taken from ref.[9]; Table 4).

Table 4. T_m data from UV melting curves (260 nm) of duplexes of d(GGATGTTCXCGA) with DNA complements carrying a mismatched base opposite X.

Mismatch[a]	T_m [°C]			
	X = d*T*[b]	X = bc-T[c]	X = bc^{ox}-T[c]	X = bc^{4,3}-T[b]
G–X	39.7 (–7.8)	37.0 (–12.0)	31.9 (–11.1)	40.4 (–6.9)
C–X	36.0 (–11.5)	35.0 (–14.0)	32.6 (–10.4)	36.3 (–11.1)
T–X	38.0 (–9.5)	32.0 (–17.0)	34.9 (–8.1)	38.6 (–8.7)

[a] Values in parentheses are ΔT_m values relative to the matched duplex. [b] T_m value for matched duplex, see Table 3. [c] T_m values for matched duplexes: bc-T: 49.0 °C, bc^{ox}-T: 43.0 °C.

As expected, a thermal destabilization of the mismatched duplexes was observed. The high mismatch discrimination observed for [3.3.0]bc-DNA is reduced in [4.3.0]bicyclo-DNA. The destabilization is generally of about the same extent as that observed with the natural mismatched duplexes. In the special case of the G–T mismatch (wobble pair), the [4.3.0]bc-T is far less destabilizing than the bc-T and the bc^{ox}-modification. From the results obtained, it can be concluded that the replacement of the "ethano" with a "propano" bridge between C(3′) and C(5′) leads to a slightly less specific pairing system with no major effect on overall affinity.

The effect of the [4.3.0]bicyclo modification on the duplex structure was studied by CD spectroscopy in the cases of ON**4** in complexation with RNA and DNA (Supporting Information). As anticipated, no major deviations in the CD spectra from those of the unmodified DNA/DNA and DNA/RNA duplexes were found, indicating no major structural changes induced by the two modified thymidine moieties in the core of the sense strand.

For comparison with tricyclo-DNA[5c] a decamer oligonucleotide bearing one [4.3.0]bc-T modification (ON**6**) was synthesized (Table 5). This modification led to a strong destabilization (–3.0 °C against DNA and –3.7 °C against RNA) of the duplex, both relative to the natural system and the tc-system (ON**7**). In contrast, the tc-T showed a stabilizing effect against its natural DNA complement. The alteration in the backbone of the [4.3.0]bicyclo system thus has an effect on the stability of the duplexes in comparison with the sequence and length of the oligonucleotide chosen.

Table 5. T_m data from UV melting curves (260 nm) of a bc^{4,3}-T and tc-T modified decamer with complementary DNA and RNA.

Code	Oligonucleotide[a]	T_m vs. DNA [°C][b]	T_m vs. RNA [°C][b]
ON**6**	d(AACTG**t**CACG)	40.3 (–3.0)	41.3 (–3.7)
ON**7**[c]	d(pAACTG$^{\mathbf{tc}}$**t**CACG)	45.3 (+0.9)[c]	43.5 (+0.5)[c]

[a] T_m of unmodified duplex: 43.3 °C (vs. DNA); 45.0 °C (vs. RNA). [b] ΔT_m per modification in parenthesis. [c] Taken from ref.[5c]; T_m is compared to natural oligonucleotides also bearing a 5′-phosphate. The values of T_m are 44.4 °C against DNA and 43.0 °C against RNA. Conditions as for Table 4.

Conclusions

We prepared the novel nucleoside [4.3.0]bicyclothymidine and incorporated this analogue into oligonucleotides through standard solid-phase synthesis. Whereas the synthesis of the analogous bc^{4,3}-ribothymidine proceeded smoothly and with high selectivity to the β-anomeric nucleoside, removal of the 2′OH function and debenzylation of **12** were the bottleneck of the synthesis, as the maximum yield of the former step remained below 40%. We believe that the difficulties of both steps are due to the high steric congestion around the C(2′,3′) centers. Because the synthesis of the parent bc-nucleosides follows a different route, we cannot compare directly the influence of the six- versus five-membered carbocyclic ring on the reactivity at these centers. It is also noteworthy that oligonucleotide synthesis, probably for the very same reason, was significantly less efficient relative to that of the parent bc-DNA. With coupling efficiencies of only around 90% the synthesis of fully modified bc^{4,3}-oligonucleotides will be extremely difficult if not impossible without improvements in the coupling step.

In order to investigate the effect of the altered backbone on the oligonucleotide level, three dodecamers bearing either one or two modified thymidine residues were synthesized and analyzed. These oligonucleotides were able to form stable duplexes both with complementary DNA and RNA and proved to be of more or less the same thermal stability as their natural counterparts. It is noteworthy that the mismatch-discrimination was lower than that in the corresponding bc-series with the five-membered carbocycle and similar to that of the natural system.

One of the aims of this work was to contribute to establishing a structure–affinity relationship of the bicyclo-DNA family and ultimately to understand the effect of conformational restriction on nucleic acid affinity. Whereas a conformational search on the bc^{4,3}-T monomer by computer simulation suggested the O(5′) substituent to adopt preferentially an equatorial orientation (with torsion angle γ being

in the *anticlinal* range), X-ray analysis of benzyl-protected precursor **12** revealed a pseudoaxial arrangement with torsion angles γ and δ that are much closer to that of the DNA backbone. Given the uncertainty that the structure of **12** in the crystal does not necessarily reflect the ground state conformation of a bc^{4,3}-nucleotide in solution, the interpretation of its effect in terms of conformational restriction remains speculative unless a high-resolution structure of a modified oligonucleotide duplex becomes available. If the ground-state conformation of the cyclohexyl ring is indeed that with the 5′-substituent in the axial position (DNA-duplex-like structure), then the change in the geometry of torsion angle γ from *anticlinal* to *gauche* had to be considered as irrelevant on duplex stability. If, however, the ground state conformation is that with the O5′-substituent in the equatorial position (DNA-duplex-unlike), then the same structural situation as in the case of bc-DNA is encountered and the potential energetic benefit for changing γ into a DNA-duplex-like geometry remains elusive. A clear conclusion, however, that can be drawn is that the shift from the bc[3.3.0]- to the bc[4.3.0]-scaffold does not dramatically alter nucleic acid affinity.

Experimental Section

General: All reactions were performed under an atmosphere of argon in dried glassware. Anhydrous solvents for reactions were obtained by filtration through activated alumina or by storage over molecular sieves (4 Å). Column chromatography (CC) was performed on silica gel (Fluka) with an average particle size of 40 μm. All solvents for CC were of technical grade and distilled prior to use. Thin-layer chromatography (TLC) was performed on silica-gel plates (Macherey–Nagel, 0.25 mm, UV_{254}). Visualization was achieved either under UV light or by staining in dip solution [vanillin (15 g), absolute ethanol (250 mL), concentrated H_2SO_4 (2.5 mL) or *p*-anisaldehyde (10 mL) concentrated H_2SO_4 (10 mL), concentrated acetic acid (2 mL), ethanol (180 mL)] followed by heating with a heat gun. NMR spectra were recorded at room temperature with a Bruker AC-300 or Bruker DRX-400 instrument. Chemical shifts (δ) are reported relative to the undeuterated residual solvent peak [$CHCl_3$: 7.27 ppm (^1H) and 77.0 ppm (^{13}C); CHD_2OD: 3.35 ppm (^1H) and 49.3 ppm (^{13}C)]. Signal assignments are based on DEPT or APT experiments, and on ^1H–^1H and ^1H–^{13}C correlation experiments (COSY/HMSC). Difference [^1H]^1H-NOE experiments were recorded at 400 MHz. Chemical shifts for ^{31}P NMR are reported relative to 85% H_3PO_4 as external standard. Electron impact (EI) spectra were recorded with a Micromass AutoSpeq Q VG with an ionization energy of 70 eV. Electrospray ionization mass spectra (ESI) were recorded with either a Fisons Instrument VG Platform (low resolution) or an Applied Biosystems, Sciex QSTAR Pulsar (high resolution). UV spectra were measured with a Varian Cary 3E UV/Vis spectrophotometer.

2: To a solution of furanose derivative **1**[12] (8.17 g, 20.94 mmol) dissolved in EtOAc (250 mL) was added H_5IO_6 (5.25 g, 23.03 mmol, 1.1 equiv.). The white suspension was stirred at room temperature under an atmosphere of argon for 90 min. Solids where then filtered off, and EtOAc was removed in vacuo. The intermediate aldehyde was dried under high vacuum for 6 h before further use. The slightly red-colored solid was taken up in anhydrous THF (150 mL) and cooled to 0 °C. Slowly, a solution of vinylmagnesium bromide (1 M in THF, 37.7 mL, 37.69 mmol, 1.8 equiv.) was added dropwise. The solution was stirred under an atmosphere of argon for 16 h and then quenched at 0 °C by the addition of ice and water. The solution was neutralized by addition of 4 M AcOH and then concentrated. The aqueous phase was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic phase was dried with $MgSO_4$, filtered, and concentrated. CC (hexane/EtOAc, 4:1) yielded diene **2** (isomeric mixture, 6.06 g, 83.6%) as a colorless oil. R_f (hexane/EtOAc, 9:1) = 0.65 (for **2***R*), 0.37 (for **2***S*). Data for **2***R*: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, Ph), 6.01 [m, 2 H, H-C(2), H-C(6′)], 5.68 [d, J = 3.78 Hz, 1 H, H-C(1′)], 5.45–5.21 [m, 4 H, H-C(7′), H-C(1)], 4.74 (m, 2 H, CH_2Ph), 4.52 [d, J = 3.75 Hz, 1 H, H-C(2′)], 4.36 [m, 1 H, H-C(5′)], 3.96 [d, J = 9.21 Hz, 1 H, H-C(4′)], 2.74 (d, J = 2.64 Hz, 1 H, OH), 2.67 [m, 2 H, H-C(3)], 1.61 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.0 (Ph_1), 132.1 [C(2)], 131.3 [C(6′)], 128.3 (Ph_{ortho}), 127.6 (Ph_{para}), 127.4 (Ph_{meta}), 119.3 [C(1)], 116.2 [C(7′)], 112.9 [C(Me_2)], 104.1 [C(1′)], 84.8 [C(3′)], 81.7 [C(4′)], 81.6 [C(2′)], 70.2 [C(5′)], 67.8 (CH_2Ph), 36.0 [C(3)], 26.8 (CH_3), 26.6 (CH_3). Data for **2***S*: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (m, 5 H, Ph), 6.02 [m, 2 H, H-C(2), H-C(6′)], 5.71 [d, J = 3.78 Hz, 1 H, H-C(1′)], 5.45–5.14 [m, 4 H, H-C(7′), H-C(1)], 4.72 (m, 2 H, CH_2Ph), 4.51 [d, J = 3.75 Hz, 1 H, H-C(2′)], 4.42 [m, 1 H, H-C(5′)], 4.12 [d, J = 6.00 Hz, 1 H, H-C(4′)], 2.67 [dd, J = 14.69, 7.61 Hz, 1 H, H-C(3)], 2.52 [dtd, J = 14.70, 6.75, 1.32, 1.32 Hz, 1 H, H-C(3)], 2.29 (d, J = 5.10 Hz, 1 H, OH), 1.60 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.8 (Ph_1), 136.7 [C(2)], 132.7 [C(6′)], 128.2 (Ph_{ortho}), 127.3 (Ph_{para}), 127.2 (Ph_{meta}), 118.8 [C(1)], 116.4 [C(7′)], 112.8 [C(Me_2)], 103.7 [C(1′)], 83.4 [C(3′)], 83.1 [C(4′)], 82.7 [C(2′)], 70.1 [C(5′)], 66.9 (CH_2Ph), 36.2 [C(3)], 26.9 (CH_3), 26.6 (CH_3) ppm. HRMS (ESI+): calcd. for $C_{20}H_{26}O_5Na$ [M + Na]$^+$ 369.1677; found 369.1676.

3 and 4: To the isomeric mixture of **2** (4.45 g, 12.85 mmol) dissolved in anhydrous CH_2Cl_2 (300 mL) was added the 2nd generation Grubbs catalyst (218.0 mg, 0.26 mmol, 2 mol-%). The slightly purple solution was stirred at 40 °C under an atmosphere of argon for 3 h. CH_2Cl_2 was then removed in vacuo, and the crude product was purified by CC (hexane/EtOAc, 7:3) to yield isomers **3** (3.13 g, 76.3%) and **4** (338.4 mg, 8.5%) as yellow oils. R_f (hexane/EtOAc, 7:3) = 0.38 (for **3**), 0.21 (for **4**). Data for **3**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 5 H, Ph), 5.92 [m, 1 H, H-C(3)], 5.68 [d, J = 3.68 Hz, 1 H, H-C(8)], 5.65 [dddd, J = 11.00, 5.43, 2.18, 1.06 Hz, 1 H, H-C(4)], 4.64 (d, J = 11.12 Hz, 1 H, CH_2Ph), 4.51 (d, J = 11.16 Hz, 1 H, CH_2Ph), 4.34 [d, J = 3.68 Hz, 1 H, H-C(7)], 4.30 [s, 1 H, H-C(1)], 4.10 [dd, J = 10.80, 3.66 Hz, 1 H, H-C(2)], 2.50 [dd, J = 18.71, 5.47 Hz, 1 H, H-C(5)], 1.89 (d, J = 10.97 Hz, 1 H, OH), 1.68 [ddd, J = 18.74, 4.83, 2.27 Hz, 1 H, H-C(5)], 1.64 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.1 (Ph_1), 131.2 [C(3)], 128.2 (Ph_{ortho}), 127.7 (Ph_{para}), 127.6 (Ph_{meta}), 123.8 [C(4)], 113.4 [C(Me_2)], 104.7 [C(8)], 81.5 [C(7)], 79.4 [C(6)], 78.1 [C(1)], 67.2 (CH_2Ph), 63.4 [C(2)], 26.8 [C(5)], 26.5 (2 × CH_3) ppm. Data for **4**: ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, Ph), 5.81 [d, J = 3.57 Hz, 1 H, H-C(8)], 5.76 [m, 1 H, H-C(3)], 5.63 [m, 1 H, H-C(4)], 4.69 (d, J = 11.31 Hz, 1 H, CH_2Ph), 4.61 (d, J = 11.31 Hz, 1 H, CH_2Ph), 4.51 [d, J = 3.03 Hz, 1 H, H-C(7)], 4.48 [d, J = 4.53 Hz, 1 H, H-C(1)], 4.41 [m, 1 H, H-C(2)], 2.49 [m, 1 H, H-C(5)], 2.18 (s, 1 H, OH), 1.79 [qd, J = 19.09, 2.77, 2.77, 2.74 Hz, 1 H, H-C(5)], 1.65 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3 (Ph_1), 128.4 (Ph_{ortho}), 128.2 [C(3)], 127.6 (Ph_{para}), 127.5 (Ph_{meta}), 123.5 [C(4)], 113.6 [C(Me_2)], 104.2 [C(8)], 82.9 [C(1)], 81.9 [C(6)], 75.8 [C(7)], 66.7 (CH_2Ph), 65.1 [C(2)], 28.0 [C(5)], 26.6 (CH_3), 26.5 (CH_3) ppm. HRMS (ESI+): calcd. for $C_{18}H_{22}O_5Na$ [M + Na]$^+$ 341.1364; found 341.1362.

5: To a solution of allyl alcohol **3** (7.84 g, 24.63 mmol) dissolved in anhydrous CH_2Cl_2 (200 mL) was added Dess–Martin periodinane (15.74 g, 36.94 mmol, 1.5 equiv.). The mixture was stirred under an atmosphere of argon at room temperature for 4 h. The solvent was removed in vacuo, and the remaining solids were taken up in EtOAc. After filtration through a bed of Celite/silica (1:1), the solvent was removed to yield the crude product. Remaining Dess–Martin reagent was removed by taking the product up in hexane/EtOAc (2:1) followed by filtration. Evaporation yielded enone **5** (7.8 g, quantitative) as a clear oil. R_f (hexane/EtOAc, 7:3) = 0.25. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 5 H, Ph), 6.84 [ddd, J = 10.27, 5.97, 2.34 Hz, 1 H, H-C(4)], 6.21 [ddd, J = 10.35, 2.08, 0.99 Hz, 1 H, H-C(3)], 5.93 [d, J = 3.59 Hz, 1 H, H-C(8)], 4.71 (d, J = 11.10 Hz, 1 H, CH_2Ph), 4.58 (d, J = 11.13 Hz, 1 H, CH_2Ph), 4.52 [d, J = 3.57 Hz, 1 H, H-C(7)], 4.32 [s, 1 H, H-C(1)], 2.80 [dd, J = 19.18, 5.98 Hz, 1 H, H-C(5)], 2.20 [td, J = 19.22, 2.89, 2.89 Hz, 1 H, H-C(5)], 2.13 [m, 1 H, H-C(5)], 1.66 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.5 [C(2)], 145.5 [C(3)], 137.8 (Ph_1), 128.8 (Ph_{ortho}), 128.3 (Ph_{ortho}), 127.7 (Ph_{ortho}), 127.3 [C(4)], 114.0 [C(Me_2)], 105.8 [C(8)], 84.8 [C(6)], 81.8 [C(1)], 81.8 [C(7)], 67.7 (CH_2Ph), 28.8 [C(5)], 26.7 (CH_3), 26.6 (CH_3) ppm. HRMS (ESI+): calcd. for $C_{18}H_{20}O_5Na$ [M + Na]$^+$ 339.1208; found 339.1196.

Luche Reduction to Enols 3 and 4: To a solution of enone **5** (7.79 g, 24.63 mmol) dissolved in anhydrous MeOH (250 mL) was added $CeCl_3{\cdot}7H_2O$ (18.35 g, 49.26 mmol, 2 equiv.). The solution was cooled to 0 °C and $NaBH_4$ (1.86 g, 49.26 mmol, 2 equiv.) was added portionwise. The clear solution was stirred at 0 °C for 30 min, and then quenched by the addition of water and neutralized with 4 M AcOH. The aqueous phase was extracted with CH_2Cl_2 (3×), and the organic phase was dried with $MgSO_4$, filtered, and evaporated to yield products **3** (2.21 g, 28.2%) and **4** (4.33 g, 55.2%).

6: To a solution of allyl alcohol **4** (4.33 g, 13.61 mmol) dissolved in anhydrous MeOH (200 mL) was added $Pd(OH)_2$/C (20 wt.-%, 866 mg) was added. The black solution was degassed with argon and then flooded with H_2 for 5 min. The solution was stirred at room temperature under an atmosphere of H_2 for 3 h. Palladium was then filtered off over Celite, and the solvent was evaporated in vacuo to yield product **6** (4.24 g, 97%) as a colorless oil. R_f (hexane/EtOAc, 7:3) = 0.44. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 5 H, Ph), 5.70 [d, J = 3.60 Hz, 1 H, H-C(8)], 4.61 (d, J = 10.74 Hz, 1 H, CH_2Ph), 4.54 (d, J = 10.92 Hz, 1 H, CH_2Ph), 4.37 [d, J = 3.57 Hz, 1 H, H-C(7)], 4.29 [d, J = 3.21 Hz, 1 H, H-C(1)], 3.80 [br. s, 1 H, H-C(2)], 1.95 (d, J = 14.31 Hz, 2 H), 1.82 (d, J = 6.96 Hz, 1 H), 1.62 (s, 3 H, CH_3), 1.55 (m, 2 H), 1.37 (s, 3 H, CH_3), 1.02 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.5 (Ph_1), 128.3 (Ph_{ortho}), 127.6 (Ph_{ortho}), 127.5 (Ph_{ortho}), 113.1 [C(Me_2)], 104.6 [C(8)], 83.5 [C(6)], 82.2 [C(7)], 78.6 [C(1)], 68.2 [C(2)], 66.4 (CH_2Ph), 29.1, 26.1, 19.2 [C(3), C(4), C(5)], 26.7 (CH_3), 26.6 (CH_3) ppm. HRMS (ESI+): calcd. for $C_{18}H_{24}O_5Na$ [M + Na]$^+$ 343.1521; found 343.1510.

7: NaH (55–65% in oil, 160.7 mg, 3.35 mmol, 2 equiv.) was dissolved in anhydrous DMF (6 mL) and cooled to 0 °C. Compound **6** (536.6 mg, 1.67 mmol) in anhydrous DMF (3 mL) was added dropwise, and the suspension was stirred at 50 °C under an atmosphere of argon for 1 h. The brown solution was then cooled to 0 °C and benzyl bromide (0.4 mL, 3.35 mmol, 2 equiv.) was added. The mixture was stirred at room temperature under an atmosphere of argon for 16 h. DMF was then removed by distillation under reduced pressure, and the yellow residue was taken up in CH_2Cl_2. The organic phase was washed with a solution of saturated aqueous $NaHCO_3$ (2×) and then dried with $MgSO_4$, filtered and concentrated. CC (hexane/EtOAc, 4:1) yielded title compound **7** (654.8 mg, 1.59 mmol, 95%) as a yellow oil. R_f (hexane/EtOAc, 7:3) = 0.58. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 10 H, Ph), 5.83 [d, J = 3.78 Hz, 1 H, H-C(8)], 4.61 (d, J = 10.20 Hz, 2 H, CH_2Ph), 4.55 (d, J = 9.6 Hz, 2 H, CH_2Ph), 4.39 [d, J = 3.21 Hz, 1 H, H-C(1)], 4.33 [d, J = 3.75 Hz, 1 H, H-C(7)], 3.64 [ddd, J = 11.50, 4.88, 3.34 Hz, 1 H, H-C(2)], 1.94 [d, J = 14.5 Hz, 1 H, H-C(3)], 1.83 [m, 1 H, H-C(6)], 1.65 (m, 1 H), 1.62 (s, 3 H, CH_3), 1.58 (m, 1 H), 1.51 (m, 1 H), 1.38 (s, 3 H, CH_3), 1.09 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7 (Ph_1), 138.5 (Ph_1), 128.2, 127.7, 127.6, 127.5, 127.3 (Ph), 112.6 [C(Me_2)], 104.8 [C(8)], 83.6 [C(6)], 81.6 [C(1)], 76.0 [C(7)], 74.9 [C(2)], 66.2 (CH_2Ph), 60.3 (CH_2Ph), 26.7 (CH_3), 26.5 (CH_3), 26.2, 25.8, 19.2 [C(3), C(4), C(5)] ppm. HRMS (ESI+): calcd. for $C_{25}H_{30}O_5Na$ [M + Na]$^+$ 433.1990; found 433.1995.

8: Compound **7** (547.5 mg, 1.33 mmol) was dissolved in 80% aqueous AcOH (25 mL) and stirred at 90 °C for 16 h. AcOH was evaporated by using EtOH (3×), toluene (3×), and anhydrous pyridine (1×) as cosolvents. The residue was dissolved in anhydrous pyridine (10 mL) and Ac_2O (10 mL) was added dropwise. The solution was stirred at room temperature under an atmosphere of argon for 16 h. It was then cooled to 0 °C and quenched by the addition of ice-cold water. The aqueous solution was extracted with CH_2Cl_2 (3×). The organic phase was washed with a solution of aqueous saturated $NaHCO_3$ (2×), dried with $MgSO_4$, and filtered, and the solvents were then evaporated. CC (hexane/EtOAc, 7:3) yielded sugar **8** (mixture of anomers, 565.4 mg, 92%) as a colorless oil. R_f (hexane/EtOAc, 7:3) = 0.53, 0.46. Data for the mixture of anomers: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 20 H, Ph), 6.46 [d, J = 4.50 Hz, 1 H, H-C(8_β)], 6.19 [s, 1 H, H-C(8_α)], 5.26 [d, J = 4.50 Hz, 1 H, H-C(7_β)], 5.12 [s, 1 H, H-C(7_α)], 4.47 [m, 10 H, 4 × CH_2Ph, H-C(1_α), H-C(1_β)], 3.67 [m, 2 H, H-C(2_α), H-C(2_β)], 2.09 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 1.82–1.70 (m, 8 H), 1.53–1.37 [m, 4 H, 2 × 2 H-C(3), 2 × 2 H-C(4), 2 × 2 H-C(5)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 169.1, 168.8, 138.5, 138.4, 128.3, 127.7, 127.6, 127.5, 127.1 (Ph), 99.9 (C-8), 95.3, 82.2, 81.1, 79.5, 78.9, 77.6, 77.4, 75.1, 74.7, 73.2, 70.7, 70.6, 66.4, 66.2, 60.3, 26.7, 25.4, 25.2, 25.1, 21.1, 20.9, 20.8, 20.5, 19.2, 19.0, 14.2 ppm. HRMS (ESI+): calcd. for $C_{26}H_{30}O_7Na$ [M + Na]$^+$ 477.1889; found 477.1882.

9: Sugar **8** (3.98 g, 8.76 mmol) and thymine (previously dried under high vacuum, 2.20 g, 17.52 mmol, 2 equiv.) were dissolved in anhydrous CH_3CN (95 mL). *N*,*O*-Bis(trimethylsilyl)acetamide (BSA) (10.7 mL, 43.8 mmol, 5 equiv.) was added dropwise, and the solution was stirred at 80 °C under an atmosphere of argon for 1 h. the mixture was then cooled to 0 °C and TMS-triflate (2.1 mL, 11.6 mmol, 1.4 equiv.) was added. The clear solution was stirred under an atmosphere of argon at 40 °C for 16 h. The solution was then cooled to 0 °C and quenched by the addition of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phase was dried with $MgSO_4$, filtered, and concentrated. CC (EtOAc/hexane, 3:2) yielded nucleoside **9** (3.01 g, 66%, 10:1 β:α) as a white foam. R_f (EtOAc/hexane, 3:2) = 0.64. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (br. s, 1 H, NH), 7.61 [d, J = 1.32 Hz, 1 H, H-C(6)], 7.35 (m, 10 H, Ph), 6.02 [d, J = 4.52 Hz, 1 H, H-C(1′)], 5.40 [d, J = 4.52 Hz, 1 H, H-C(2′)], 4.72 (d, J = 12.12 Hz, 1 H, CH_2Ph), 4.64 (d, J = 11.96 Hz, 1 H, CH_2Ph), 4.56 (d, J = 11.36 Hz, 1 H, CH_2Ph), 4.48 (d, J = 11.48 Hz, 1 H, CH_2Ph), 4.29 [d, J = 3.80 Hz, 1 H, H-C(4′)], 3.86 [m, 1 H, H-C(5′)], 2.06 (s, 3 H, OAc), 1.84 [m, 4 H, H-C(6′), H-C(8′)], 1.70 [d, J = 1.12 Hz, 3 H, C(5)-CH_3], 1.65 [m, 1 H, H-C(7′)], 0.88 [m, 1 H, H-C(7′)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 143.1, (thymine and acetoxy), 138.7 (Ph_1), 138.5 (Ph_1), 135.8 [C(6)], 128.6,

128.4, 128.1, 127.9, 127.7, 127.5, 126.9 (phenyl), 121.3, 110.7 [C(1′)], 103.2, 80.3, 76.3, 74.5, 70.7, 66.8, 66.3, 60.8, 27.5, 25.6, 21.4, 20.8, 12.5, 12.2 ppm. HRMS (ESI+): calcd. for $C_{29}H_{32}O_7N_2Na$ $[M + Na]^+$ 543.2107; found 543.2116.

10: To a solution of nucleoside **9** (171.2 mg, 0.33 mmol) dissolved in anhydrous MeOH (4 mL) was added sodium methoxide (35.5 mg, 0.66 mmol, 2 equiv.). The clear solution was stirred under an atmosphere of argon at room temperature for 16 h. After cooling to 0 °C, the solution was quenched by the addition of 1 M aqueous HCl and then extracted with CH_2Cl_2 (3×). The organic phase was washed with a solution of saturated aqueous $NaHCO_3$ and then dried with $MgSO_4$, filtered, and concentrated. CC (EtOAc/hexane,3:2) yielded compound **10** (128.4 mg, 0.27 mmol, 82%) as a white foam. R_f (EtOAc/hexane, 3:2) = 0.42. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (br. s, 1 H, NH), 7.68 [d, J = 1.24 Hz, 1 H, H-C(6)], 7.34 (m, 10 H, Ph), 5.93 [d, J = 5.24 Hz, 1 H, H-C(1′)], 4.61 (m, 4 H, 2 × CH_2Ph), 4.33 [d, J = 4.40 Hz, 1 H, H-C(4′)], 4.24 [dd, J = 7.36, 5.52 Hz, 1 H, H-C(2′)], 3.92 [ddd, J = 7.20, 4.30, 2.94 Hz, 1 H, H-C(5′)], 3.19 (d, J = 7.32 Hz, 1 H, OH), 1.95 [m, 2 H, H-C(6′)], 1.77 [m, 2 H, H-C(8′)], 1.57 [d, J = 1.12 Hz, 3 H, C(5)-CH_3], 1.33 [d, J = 1.08 Hz, 1 H, H-C(7′)], 0.88 [m, 1 H, H-C(7′)] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.3, 151.1 (quart. thymine), 137.9 (Ph_{quart}), 135.8 [C(6)], 128.7–126.1 (phenyl), 110.5 [C(5)], 90.7 [C(1′)], 82.1 [C(3′)], 79.1 [C(4′)], 77.0 [C(2′)], 74.7 [C(5′)], 70.1 (CH_2Ph), 65.6 (CH_2Ph), 26.8 [C(8′)], 25.7 [C(6′)], 16.9 [C(7′)], 12.0 [C(5)-CH_3] ppm. ^{1}H NMR difference-NOE (400 MHz, $CDCl_3$): δ (%) = 5.93 → 4.33 (2.2), 4.24 (2.1); 4.24 → 7.68 (6.7), 5.93 (3.0), 1.95 (1.1), 1.33 (4.0); 3.92 → 7.24 (3.1), 4.61 (6.6), 4.33 (9.3), 1.95 (1.6), 1.33 (1.1); 3.19 (OH) → 5.93 (9.1), 4.24 (5.6) ppm. HRMS (ESI+): calcd. for $C_{27}H_{30}N_2O_6Na$ $[M + Na]^+$ 501.2001; found 501.1992.

11: Nucleoside **10** (1.74 g, 3.63 mmol) was dissolved in anhydrous DMF (35 mL) and treated with 1,1′-thiocarbonyldiimidazole (971.5 mg, 5.45 mmol, 1.5 equiv.). The yellow solution was stirred at room temperature under an atmosphere of argon for 6 h. DMF was evaporated, and the yellow oil was taken up in water. Extraction with CH_2Cl_2 (3×) was followed by drying over $MgSO_4$ and filtration. After concentration, CC (1:1 EtOAc/hexane) yielded compound **11** (2.01 g, 94%) as a white foam. R_f (EtOAc/hexane, 1:1) = 0.11. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.31 [s, 1 H, H-C(imidazole)], 7.88 (br. s, 1 H, NH), 7.71 [d, J = 1.32 Hz, 1 H, H-C(6)], 7.58 [t, J = 3.00, 1.68 Hz, 1 H, H-C(imidazole)], 7.37 (m, 10 H, Ph), 7.02 [dd, J = 1.71, 0.96 Hz, 1 H, H-C(imidazole)], 6.41 [s, 2 H, H-C(2′), H-C(1′)], 4.82 (d, J = 11.85 Hz, 1 H, CH_2Ph), 4.62 (m, 3 H, CH_2Ph), 4.33 [d, J = 4.35 Hz, 1 H, H-C(4′)], 4.03 [m, 1 H, H-C(5′)], 2.07–1.97 [m, 4 H, 2 × CH_2, H-C(6′), H-C(8′)], 1.62 [m, 2 H, CH2, H-C(7′)], 1.48 [d, J = 0.93 Hz, 3 H, C(5)-CH_3] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 222.0 (C=S), 154.8, 137.9 (Ph_{quart}), 137.4, 135.7, 128.7, 128.7, 128.5, 128.1, 127.8, 127.2, 126.8, 111.1, 82.3, 80.8, 74.6, 707, 66.3, 31.4, 27.3, 11.8 ppm. HRMS (ESI+): calcd. for $C_{31}H_{32}N_4O_6S$ $[M]^+$ 589.6924; found 589.1404.

12: Thioester **11** (3.9 g, 6.63 mmol) was dissolved in toluene (100 mL) and flooded with argon for 15 min. AIBN (544 mg, 3.31 mmol, 0.5 equiv.) was then added, and the solution was again flushed with argon. Bu_3SnH (3.50 mL, 13.25 mmol, 2 equiv.) was then added dropwise, and the clear solution was stirred at 80 °C under an atmosphere of argon for 4 h. Another portion of AIBN (544 mg, 3.31 mmol, 0.5 equiv.) and of Bu_3SnH (1.75 mL, 6.63 mmol, 1 equiv.) was added, and the solution was stirred for another 12 h. Toluene was evaporated in vacuo followed by CC (1:1 EtOAc/hexane) to give compounds **12** (1.14 g, 37.2%) as a white solid and **11** (920.8 mg, 23.5%), and **10** (593.4 mg, 18.7%) as white foams. Data for **12**: R_f (EtOAc/hexane, 1:1) = 0.38. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (br. s, 1 H, NH), 7.72 [d, J = 1.20 Hz, 1 H, H-C(6)], 7.35 (m, 10 H, Ph), 6.21 [dd, J = 7.60, 6.01 Hz, 1 H, H-C(1′)], 4.59 (2 × dd, 4 H, 2 × CH_2Ph), 4.12 [d, J = 4.44 Hz, 1 H, H-C(4′)], 3.93 [m, 1 H, H-C(5′)], 2.70 [dd, J = 13.08, 5.92 Hz, 1 H, H-C($2'_{eq}$)], 2.14 [dd, J = 13.08, 7.60 Hz, 1 H, H-C($2'_{ax}$)], 1.95–1.31 [m, 6 H, H-C(6′), H-C(7′), H-C(8′)], 1.56 [d, J = 0.78 Hz, 3 H, C(5)-CH_3] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.3, 151.1 (quart. thymine), 137.9 (Ph_{quart}), 136.2 [C(6)], 128.7–126.1 (phenyl), 110.5 [C(5)], 84.8 [C(1′)], 83.3, 75.0 [C(4′), C(5′)], 70.6 (CH_2Ph), 64.8 (CH_2Ph), 40.4 [C(2′)], 30.1, 25.2, 17.1 [C(6′), C(7′), C(8′)], 12.1 [C(5)-CH_3] ppm. HRMS (ESI+): calcd. for $C_{27}H_{30}N_2O_5Na$ $[M + Na]^+$ 485.2025; found 485.2059.

13: Compound **12** (85 mg, 0.18 mmol) was dissolved in anhydrous MeOH (5 mL) and degassed with argon. $Pd(OH)_2$/C (20%, 55 mg) and cyclohexa-1,4-diene (0.17 mL, 1.84 mmol, 10 equiv.) were then added. The black solution was once again degassed with argon and then flushed with H_2. The solution was stirred under an atmosphere of H_2 at room temperature for 6 h. Palladium residues were filtered and washed with MeOH. The solvent was evaporated, and the crude product was purified by CC (CH_2Cl_2/MeOH, 95:5) to yield monomer **13** (28.3 mg, 55%) as a white solid. R_f (CH_2Cl_2/MeOH, 95:5) = 0.15. ^{1}H NMR (400 MHz, MeOD): δ = 8.20 [d, J = 1.17 Hz, 1 H, H(6)], 6.22 [dd, J = 7.72, 6.24 Hz, 1 H, H-C(1′)], 4.03 [dtd, J = 4.37, 4.37, 6.30, 6.45 Hz, 1 H, H-C(5′)], 3.80 [d, J = 4.43 Hz, 1 H, H-C(4′)], 2.19 [ddd, J = 18.95, 12.73, 6.98 Hz, 2 H, H-C(2′)], 1.91–1.86 (m, 1 H), 1.89 [d, J = 1.20 Hz, 3 H, C(5)-CH_3], 1.78–1.49 [m, 5 H, H-C(6′), H-C(7′), H-C(8′)] ppm. ^{13}C NMR (101 MHz, MeOD): δ = 163.3, 151.1 (quart. thymine), 139.0 [C(6)], 110.5 [C(5)], 86.3 [C(4′)], 86.0 [C(1′)], 78.5 [C(3′)], 68.4 [C(5′)], 44.8 [C(2′)], 36.0, 30.8, 18.3 [C(6′), C(7′), C(8′)], 12.5 [C(5)-CH_3] ppm. ^{1}H NMR difference-NOE (400 MHz, MeOD): δ (%) = 8.20 → 6.22 (2.0), 4.03 (0.7), 3.80 (0.4), 2.21 (4.1), 1.89 (7.6); 6.22 → 8.20 (1.7), 3.80 (2.8), 2.16 (5.6); 4.03 → 8.20 (0.9), 3.80 (10.3), 1.60 (1.6); 3.80 → 6.22 (3.3), 4.03 (8.9); 2.21 → 8.20 (9.3), 6.22 (4.1), 2.16 (8.5); 2.16 → 6.22 (12.7), 3.80 (1.3), 2.21 (7.8) ppm. HRMS (ESI+): calcd. for $C_{13}H_{18}N_2O_5Na$ $[M + Na]^+$ 305.1113; found 305.1121.

14: Nucleoside **13** (210 mg, 0.74 mmol) was coevaporated with anhydrous benzene (3 mL) and pyridine (3 mL). It was then taken up again in anhydrous pyridine (3 mL) and (4,4′-dimethoxytriphenyl) methyl triflate (DMTOTf, 510 mg, 1.13 mmol, 1.5 equiv.) was added. The red-brown solution was stirred at room temperature under an atmosphere of argon for 3 h and then another portion of DMTOTf (170 mg, 0.38 mmol, 0.5 equiv.) was added. After 7 h, a third portion of DMTOTf (170 mg, 0.38 mmol, 0.5 equiv.) was added, and the solution was stirred for another 12 h. The reaction was then quenched by the addition of a solution of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3×), and the organic phase was dried with $MgSO_4$, filtered, and concentrated. CC (EtOAc/hexane, 9:1 + 1% Et_3N) yielded nucleoside **14** (282.6 mg, 65%) as a yellow foam. R_f (EtOAc/hexane, 9:1) = 0.22. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H, NH), 7.57 [d, J = 1.22 Hz, 1 H, H-C(6)], 7.55 (m, 2 H, arom.), 7.46–7.43 (m, 4 H, arom.), 7.32–7.23 (m, 3 H, arom.), 6.85 (s, 2 H, arom.), 6.83 (s, 2 H, arom.), 5.87 [dd, J = 7.81, 4.70 Hz, 1 H, H-C(1′)], 3.83 [m, 1 H, H-C(5′)], 3.81 (s, 6 H, PhMeO), 3.15 [d, J = 3.51 Hz, 1 H, H-C(4′)], 2.31 [dd, J = 13.75, 7.86 Hz, 1 H, H-C($2'_{\alpha}$)], 1.96 [dd, J = 14.70, 9.98 Hz, 1 H, H-C($2'_{\beta}$)], 1.91 [d, J = 1.20 Hz, 3 H, C(5)-CH_3], 1.51–1.31 and 0.91–0.84 [m, 6 H, H-C(6′), H-C(7′), H-C(8′)] ppm. ^{13}C NMR (101 MHz, MeOD): δ = 163.2 (C=O), 158.7 (C-O-CH_3), 149.8, 145.7, 136.8 (C_{ar}), 135.2 [C(6)], 130.4, 129.3, 128.5, 128.3, 127.8, 126.9 (C_{ar}), 113.1 (C_{ar}), 110.2 [C(5)], 86.9 [C(3′)], 83.5

[C(1′)], 83.0 [C(4′)], 70.1 [C(5′)], 55.2 (O-CH_3), 47.4 [C(2′)], 35.1 [C(8′)], 27.3 [C(7′)], 19.8 [C(6′)], 12.7 [C(5)-CH_3] ppm. HRMS (ESI+): calcd. for $C_{43}H_{36}N_2O_7Na$ $[M + Na]^+$ 607.2420; found 607.2439.

15: DMT-protected nucleoside **14** (275.0 mg, 0.47 mmol) was dissolved in anhydrous benzene (3 mL) and the solvent was evaporated. It was then taken up in anhydrous CH_3CN (3 mL) and Hünig's base (0.40 mL, 2.36 mmol, 5 equiv.) and freshly distilled 2-cyanoethoxydiisopropylaminochlorophosphane (CEPCl, 0.32 mL, 1.43 mmol, 3 equiv.) were added. The yellow solution was stirred at room temperature under an atmosphere of argon for 2 h and then diluted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ (1×) and the aqueous phase was extracted with EtOAc (2×). The combined organic phase was dried with $NaSO_4$, filtered, and concentrated. CC (EtOAc/hexane, 2:1 + 1% Et_3N) yielded phosphoramidite **15** (260 mg, 70%) as a white foam. R_f (EtOAc/hexane, 4:1) = 0.47. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (br. s, 1 H, NH), 7.57 [dd, J = 2.21, 1.23 Hz, 1 H, H-C(6)], 7.53 (m, 3 H, arom. DMT), 7.44–7.40 (m, 4 H, arom. DMT), 7.30–7.21 (m, 2 H, arom. DMT), 6.82 (s, 2 H, arom.), 6.82 (s, 2 H, arom.), 5.94 [ddd, J = 18.91, 8.01, 4.32 Hz, 1 H, H-C(1′)], 3.83 [m, 1 H, H-C(5′)], 3.80 (s, 6 H, PhMeO), 3.68 [m, 1 H, H-C(4′)], 3.52 (m, 4 H, 2× H-C_{iPr}, OCH_2), 2.73 [dd, J = 13.81, 8.24 Hz, 1 H, H-C(2′$_\beta$)], 2.53 (m, 2 H, CH_2CN), 1.96 [m, 1 H, H-C(2′$_\alpha$)], 1.91 [dd, J = 7.41, 1.00 Hz, 3 H, C(5)-CH_3], 1.43–1.20 and 0.88–0.84 [m, 6 H, H-C(6′), H-C(7′), H-C(8′)], 1.12 [dd, J = 6.77, 2.06 Hz, 6 H, $(CH_3)_2CH$], 1.03 [dd, J = 12.06, 6.77, (CH Hz, 6 $H_3)_2CH$] ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.3 (C=O), 158.7 (C-O-CH_3), 149.9, 145.8, 136.9, 136.8 (C_{ar}), 135.3, 135.2 [C(6)], 130.4, 130.3, 128.4, 127.7, 126.8 (C_{ar}), 117.7, 117.6 (CN), 113.0 (C_{ar}), 110.2 [C(5)], 86.8, 86.7 [C(3′)], 84.1, 83.9 [C(1′)], 83.3, 83.2 [C(4′)], 77.3, 77.3 [C(Ph_3)], 70.2 [C(5′)], 57.7, 57.6, 57.5, 57.4 (OCH_2), 55.2 (OCH_3), 45.0, 44.9 [C(2′)], 43.3, 43.2, 43.1, 43.0 (C_{iPr}), 34.7 [C(8′)], 27.4, 27.3 [C(7′)], 24.5, 24.4, 24.3, 24.2 (H_3C_{iPr}), 20.4, 20.3, 20.3, 20.2 (CH_2-CN), 19.8, 19.7 [C(6′)], 12.7 [C(5)-CH_3] ppm. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ = 142.90, 140.87 ppm. HRMS (ESI+): calcd. for $C_{43}H_{53}N_4O_8NaP$ $[M + Na]^+$ 807.3498; found 807.3494.

Molecular Modeling: The conformational search was performed in an MM^+ force field with the conformational search software (HyperChem Conformational Search, Version 8.0) as included in HyperChem™ Professional 8.0.4. Torsion angles of the six-membered ring as well as γ and δ were varied. The standard parameter set up was used. The structures were energy minimized to a RMS gradient of 0.01 kcal Å^{-1} mol^{-1}. Wrong chirality structures were discarded.

Energy minimizations for duplexes, were carried out with the Amber force field as incorporated in the software package HyperChem™ Professional 8.0.4. Explicit H_2O molecules and counterions were not included. A distance-dependent permittivity of $\varepsilon = 4r$ was used instead as a screening function. The double helical structure was built on the basis of the parameters of a B-DNA. It was minimized by using a Polak–Ribiere algorithm with an RMS gradient of 0.01 kcal Å^{-1} mol^{-1}.

Oligonucleotide Synthesis and Purification: The chemical synthesis of oligonucleotides was performed either on a 1.3 μmol scale with a Pharmacia LKB Gene Assembler Special DNA-synthesizer or on a 1 μmol scale with a Polygen DNA synthesizer by using standard phosphoramidite chemistry. The phosphoramidite building blocks of the natural nucleosides and the nucleosides bound to CPG-solid support were purchased from Glen Research or Vivotide. Solvents and reagents used for the synthesis were prepared according to the indications of the manufacturer. 5-(Ethylthio)-1*H*-tetrazole (ETT) was used as an activator and 3% dichloroacetic acid in dichloroethane was used for detritylation. The concentrations for the natural phosphoramidite solutions were 0.1 M and for the modified phosphoramidites 0.15 M or 0.2 M. The coupling times for natural phosphoramidites were 1.5 min and for the modified phosphoramidite 12–14 min. The coupling efficiencies for **15** were generally low (≈90%) as judged from the trityl assay. Deprotection and detachment of the oligonucleotides were performed in concentrated NH_3 (0.5 mL, 55 °C, 16 h). RNA oligonucleotides were instead treated with concentrated NH_3/EtOH (3:1, 0.5 mL, 55 °C, 30 h) then evaporated before TBAF (0.5 mL) was added (room temp., 24 h). After evaporation, the brown deposit was taken up in H_2O then filtered through a SEP-PACK® C-18 cartridge (Waters). The crude samples were purified by either RP-HPLC (Source 15 RPC ST 100/4.6 Polystyrene-15 column from Pharmacia Biotech or VA 15/4.6 Nucleogel RP 300–5 column from Macherey–Nagel) or ion exchange–HPLC (DNAPac-200 4 × 250 mm column with precolumn both from Dionex). Samples from ion-exchange HPLC were desalted over SEP-PACK® C-18 cartridge (Waters) according to the protocol of the manufacturer. The following buffers were used for HPLC: RP-HPLC: A: 0.1 M triethylammonium acetate in H_2O, pH 7.0; B: 0.1 M triethylammonium acetate in H_2O/CH_3CN (1:4), pH 7. DEAE–HPLC: A: 20 mM KH_2PO_4 in H_2O/CH_3CN (4:1), pH 6.0; B: 20 mM KH_2PO_4, 1 M KCl in H_2O/CH_3CN (4:1), pH 6.0. Linear gradients of B in A were used. The integrity of all oligonucleotides was confirmed with MS (ESI–; see Supporting Information). Concentrations of the oligonucleotide solutions were determined by UV absorption at 260 nm.

Melting Curves: Thermal denaturation experiments were carried out with a Varian Cary 3E UV/Vis spectrophotometer. Absorbances were monitored at 260 nm and the heating rate was set to 0.5 °C min^{-1}. A cooling–heating–cooling cycle in the temperature range of 80–15 °C was applied. The first derivative of the melting curves were calculated with the Varian WinUV software. To avoid evaporation of solvents, a layer of dimethylpolysiloxane was added over the samples within the cell. All measurements were carried out in NaCl (150 mM)/Na_2HPO_4 (10 mM) at pH 7.0 at a total oligonucleotide concentration of 2 μM.

CCDC-705765 (for **12**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Structure refinement details; UV melting curves; CD spectra.

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