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Synthesis and Structural Study of *ribo*-Dioxaphosphorinane-Constrained Nucleic Acid Dinucleotides (*ribo*-α,β-D-CNA)

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With increasing interest in the control of the conformations of nucleic acids to define active riboswitch or siRNA, we present herein our efforts towards the stereocontrolled synthesis and conformational analysis of ribodinucleotides in which α and β torsional angles are constrained within a dioxaphosphorinane structure (*ribo*-α,β-D-CNA). The crystal structure analysis of one α,β-D-CNA TU dimer demonstrates the absolute stereochemistry of the newly created asymmetric centres. NMR and CD analyses allowed complete assignment and the determination of the torsional angles in the α,β-D-CNA UU diastereoisomers.

Introduction

Many biologically important nucleic acids exhibit unusual conformations of the sugar/phosphate backbone torsional angles α–ζ that lead to structural distortions either of the double helix or of the single strand (Figure 1). These structures are very often specifically involved in particular macromolecular processes.[1] X-ray data analyses of biologically important RNAs have shown that many torsional angles deviate from the regular values observed in A- or B-type duplexes.[2,3] Unfortunately, experimental studies aimed at determining the structural and functional implications of such helical deformations are somewhat complicated by the intrinsically transient nature of the corresponding backbone states. Stable structural analogues of these distorted backbone geometries would be very useful in the elucidation of the role that helical deformations play in nucleic acid reactivity and interactions. Much effort has been devoted to the elaboration of modified nucleotide analogues that are conformationally constrained for therapeutic purposes.[4] More recently, the discovery of the riboswitch and siRNA has strengthened the interest in chemically modified oligonucleotides.[5] However, the main effort has been directed towards defining analogues with a high affinity for nucleic acid targets, biostability, and efficient cellular uptake. On the other hand, little attention has been devoted to the design and elaboration of constrained nucleotides with a view to controlling the shape of the sugar/phosphate backbone of nucleic acids.[6] Therefore, in this context, it is of interest to elaborate modified nucleotides that could help in folding control or that could mimic biologically important local distortion of nucleic acids.

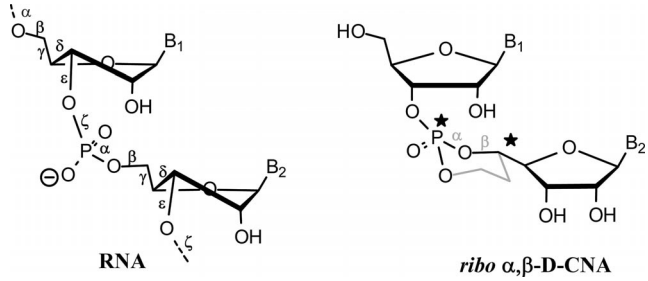

Figure 1. Left: the six backbone torsion angles (labelled α to ζ) of nucleic acids. Right: the α,β-D-CNA unit is a dinucleotide in which α and β are controlled to canonical or noncanonical values by a dioxaphosphorinane ring structure exhibiting two new asymmetric centres.

With this in mind, we have developed and reported on the construction of covalently constrained nucleic acid (CNA) building blocks in which the backbone torsion angles are part of a dioxaphosphorinane ring structure in the DNA series (2′-deoxyribose).[7] Herein we disclose the detailed synthesis and structural study of ribose α,β-D-CNA dinucleotides (Figure 1) in which the α and β torsional angles can adopt either the canonical [*gauche*(–),

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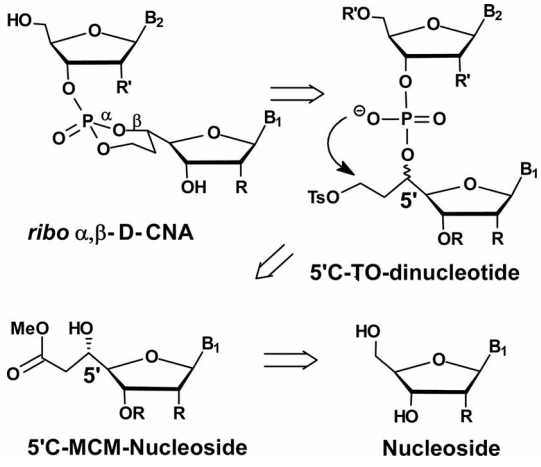
trans] conformation found in A- or B-type duplexes[3] or the non-canonical [*gauche*(+), *trans*] combination frequently found in bulged regions of nucleic acids.[8,9]

Results and Discussion

The retrosynthetic analysis for the preparation of both stereoisomers of *ribo*-α,β-D-CNA dinucleotides is summarised in Scheme 1. The formation of the dioxaphosphorinane ring is based on a very simple strategy that involves the attack of the phosphate oxyanion on an electrophilic tosyloxy-substituted carbon atom. The linear dinucleotide precursors with 5′-*C*-(tosyloxyethyl) substitution can be easily obtained according to standard phosphoramidite technology by coupling commercially available phosphoramidites with 5′-*C*-(tosyloxyethyl) nucleosides. The latter can be prepared from 5′-*C*-methoxycarbonylmethyl nucleosides, which can be synthesised by a Mukaiyama-type aldolisation reaction of the corresponding 5′-*C*-aldehyde nucleosides.

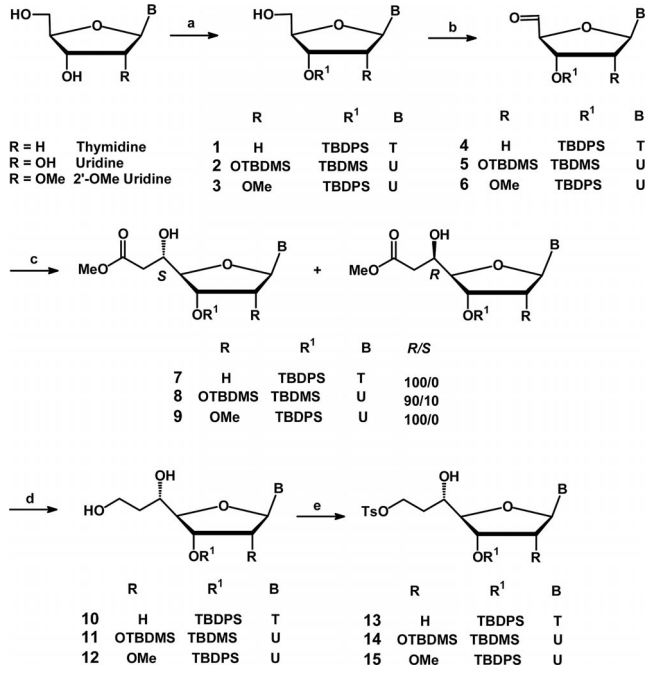


Scheme 1. Retrosynthetic analysis for the preparation of *ribo*-α,β-D-CNA.

This methodology has been successfully applied to the synthesis of α,β-D-CNA starting from 2′-deoxy-*ribo*-thymidine.[10] However, in the ribose nucleoside series a few points remain to be addressed: 1) the behaviour of the dioxaphosphorinane structure in the presence of a 2′-hydroxy functionality on the upstream nucleoside, 2) the stereocontrol of the newly created asymmetric centres (5′-carbon and phosphorus) and 3) the influence of the neutral dioxaphosphorinane internucleotidic linkage.

To provide an insight into these questions, we investigated the synthesis of the three following dimer combinations: *ribo*/2′-deoxy-*ribo*-, 2′-deoxy-*ribo*/*ribo*- and *ribo*/*ribo*-α,β-D-CNA on the ribose puckering.

In the first step we had to prepare two 5′-*C*-(tosyloxyethyl)uracils **14** and **15** differentiated by the 2′- and 3′-*O*-protecting groups, as shown in Scheme 2 (together with the previously described (*S*)-5′-*C*-(tosyloxyethyl)thymidine **13**[11]). They were obtained from the corresponding diastereopure diols **11** and **12** by selective tosylation with tosyl chloride in the presence of pyridine and chloroform in moderate-to-good yields.[12] The diastereomerically pure diols were prepared in yields of 80–95% by reduction of the ester function of 5′-*C*-methoxycarbonylmethyl-uridines **8** and **9** with $NaBH_4$. A diastereoselective Mukaiyama reaction of the corresponding 5′-*C*-aldehyde uridines **5** and **6** with the silyl ketene of methyl acetate catalysed by $BiCl_3/ZnI_2$[13] gave access to **8** with a 9:1 ratio in favour of the 5′*S* isomer whereas **9** was obtained as the pure 5′*S* diastereoisomer. The bulky 3′-*O*-*tert*-butyldiphenylsilyl protecting group on the aldehyde seems to be responsible for the high selectivity achieved in the addition to **4** and **6** in comparison with **5** in which it is replaced by the smaller *tert*-butyldimethylsilyl group.

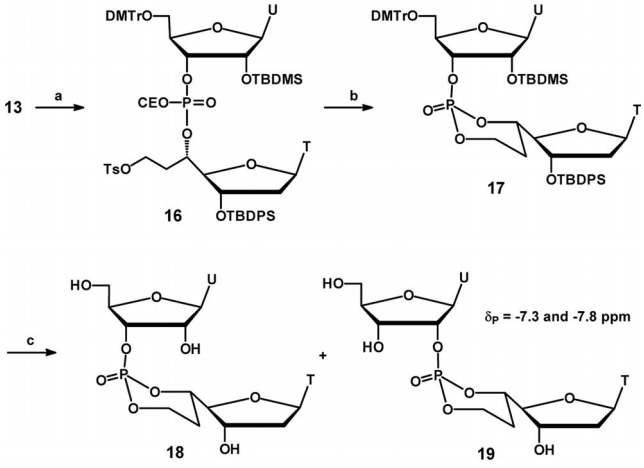


Scheme 2. Synthesis of 5′-*C*-tosyloxy nucleosides. Reagents: a) i. TBDMSCl, Py, 95%; ii. TBDPSCl or TBDMSCl, DMF, Imid, 90%; iii. PTSA, MeOH, 95%; b) DCC, DMSO, DCAA, then oxalic acid, 60–90%; c) methyl acetate silyl ketene, $BiCl_3/ZnI_2$, DCM, 65–90%; d) $NaBH_4$, EtOH, 80–95%; e) TsCl, Py, $CHCl_3$, 55–86%.

The absolute configurations at the chiral C-5′ centre were not determined at this stage but in a structural analysis of the corresponding synthesised D-CNA. Note that the stereochemical outcome of this nucleophilic addition is opposite to the stereochemistry depicted in the synthesis of Tunicamycin involving the addition of allyltrimethylsilane to a similar aldehyde in the presence of BF_3 etherate.[14]

The 5′-*C*-aldehyde nucleosides **5**[15] and **6** were prepared by a Pfitzner–Moffatt oxidation procedure[16] of the 5′-hydroxy function of 2′,3′-*O*-protected uridines **2** and **3** in moderate-to-good yields and used in the subsequent step without further purification. Starting from 2′-*O*-methyluridine or uridine, the protected derivatives **2** and **3** were synthesised in three steps by selective silylation protection/deprotection in high yields.[17]

With the three 5′-*C*-(tosyloxyethyl) nucleosides **13**–**15** in hand we synthesised *ribo*-α,β-D-CNA according to the methodology developed for 2′-deoxy-*ribo*-α,β-D-CNA (Scheme 3).[11]



Scheme 3. Synthesis of *ribo*/2′-deoxy-*ribo*-α,β-D-CNA UT. Reagents: a) 2′-OTBDMS uridine phosphoramidite, tetrazole, CH_3CN then I_2/H_2O/Coll, 71%; b) K_2CO_3, DMF, 92%; c) i. NEt_3, 3 HF, THF, 85%; ii. 3% TFA/CH_2Cl_2, 80%.

As expected, the acyclic dinucleotide **16** precursor of *ribo*/2′-deoxy-*ribo*-α,β-D-CNA was assembled by standard phosphoramidite technology[18] by coupling the commercially available 2′-*O*-(*tert*-butyldimethylsilyl)uridine phosphoramidite to 5′-*C*-(tosyloxyethyl)thymidine **13** in 71% yield. Dioxaphosphorinane ring formation mediated by K_2CO_3 in DMF occurred in good yield (92%) with very high diastereoselectivity and only compound **17** was detected by ^{31}P NMR (δ = –8.5 ppm). Attempts to remove the silyl protecting groups with TBAF failed and only furnished mixtures with no detectable dioxaphosphorinane ring by ^{31}P NMR spectroscopy. Treatment with the mild reagent NEt_3·3HF in THF at room temperature for 24 h provided a compound with a single peak at δ_P = –7.9 ppm that proved to be unstable over time. After removal of the 5′-*O*-DMTr protecting group in an acidic medium, a mixture of two compounds was isolated and characterised by ^{31}P NMR with the signals at –7.8 and –7.3 ppm (2:1 ratio) corresponding to the dioxaphosphorinane structures. However, efforts to separate them by reversed-phase HPLC (retention times of 6.5 and 9 min) showed that each isolated fraction provided the same chromatogram (two peaks with the same ratio and retention times), which is indicative of an equilibrium between the proposed compounds **18** and **19**.

Therefore we concluded that the presence of the free 2′-hydroxy function on the upper nucleoside induced instability in this UT D-CNA series. DFT calculations clearly evidenced that the expected α,β-D-CNA UT can adopt a geometry in which the 2′-hydroxy function of the upper uridine, the phosphorus atom and the 5’-oxygen of the lower thymidine are in line (Figure 2). This particular conformation, induced by the dioxaphosphorinane ring, can strongly favour a transesterification process, which could be responsible for the observed instability and further degradation of the target compound. This particular in-line geometry is typically observed within the hammerhead ribozyme at the active site during intramolecular phosphodiester cleavage.[19]

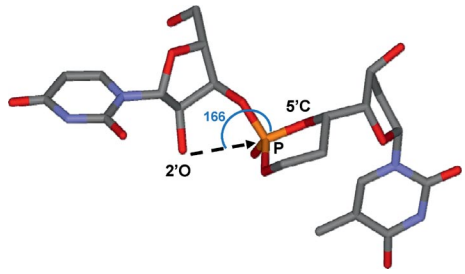
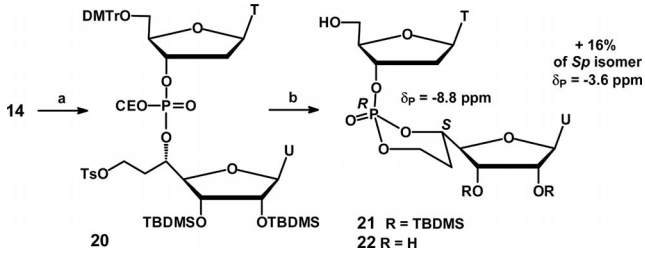


Figure 2. Results of the DFT calculation evidencing the in-line conformation of α,β-D-CNA UT **18**.

2′-Deoxy-*ribo*/*ribo*-α,β-D-CNA TU **21** was readily synthesised in three steps in 47% overall yield from 5′-*C*-(tosyloxyethyl)uridine **14** by phosphoramidite coupling with standard thymidine phosphoramidite followed by K_2CO_3-mediated dioxaphosphorinane ring formation and removal of the 5′-*O*-protecting group in TFA (Scheme 4). However, the cyclisation process did not occur with high diastereoselectivity (5.3:1 ratio) with 16% of the minor S_P isomer being formed, as depicted by ^{31}P NMR (δ = –3.8 ppm). The two diastereoisomers were easily separable by silica gel chromatography. At this level the determination of the absolute configurations at the newly created C-5′ and P asymmetric centres of **14** and α,β-D-CNA TU **21** was greatly simplified by the X-ray structure solved for the latter (Figure 3).



Scheme 4. Synthesis of 2′-deoxy-*ribo*/*ribo*-α,β-D-CNA TU. Reagents: a) thymidine phosphoramidite, tetrazole, CH_3CN then I_2/H_2O/coll., 70%; b) i. K_2CO_3, DMF, 95%; ii. 3% TFA/$CH_2Cl_2$to give **21**, 85% and iii. TBAF, THF to give **22**, 79%.

This crystal structure gives further evidence that the C-5′ atom of the modified uridine is *S*-configured allowing the assignment of the absolute configuration of **14** and thus indicating the stereochemical outcome of the Mukaiyama reaction of 5′-*C*-aldehyde uridine **5** (Scheme 2). The X-ray structure also revealed that the six-membered cyclic phosphotriester adopts the chair conformation with non-canonical dihedral values of α = +68.9° and β = +176.1°. Surprisingly, in the solid state, the thymidine sugar moiety features C-2′ *exo* puckering, which is unexpected due to the presence of the neutral internucleotidic linkage.

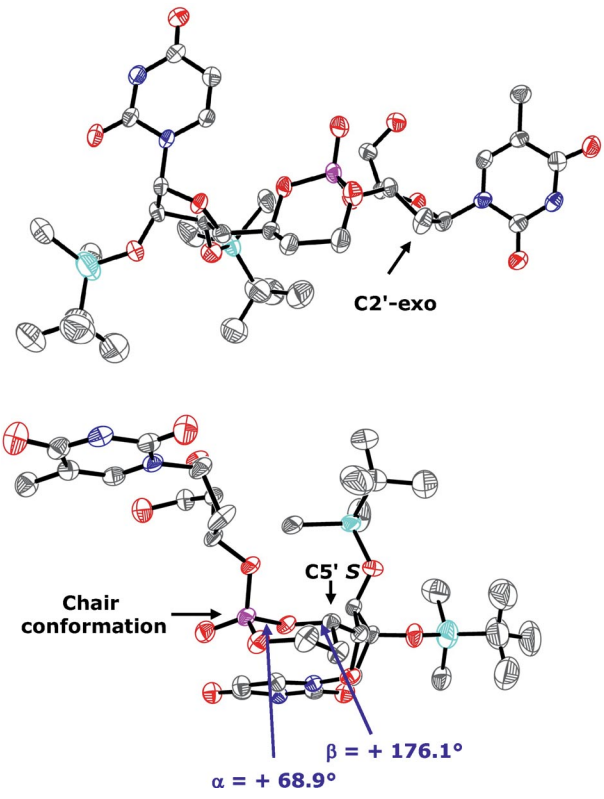


Figure 3. X-ray molecular structure of the ($S_{C5'}$,R_P)-configured α,β-D-CNA TU dimer **21** displaying the chair and C-2′ *exo* conformations of the dioxaphosphorinane and sugars subunits. For clarity, hydrogen atoms and co-crystallised solvent molecules have been omitted. Thermal ellipsoids are shown at the 40% probability level.

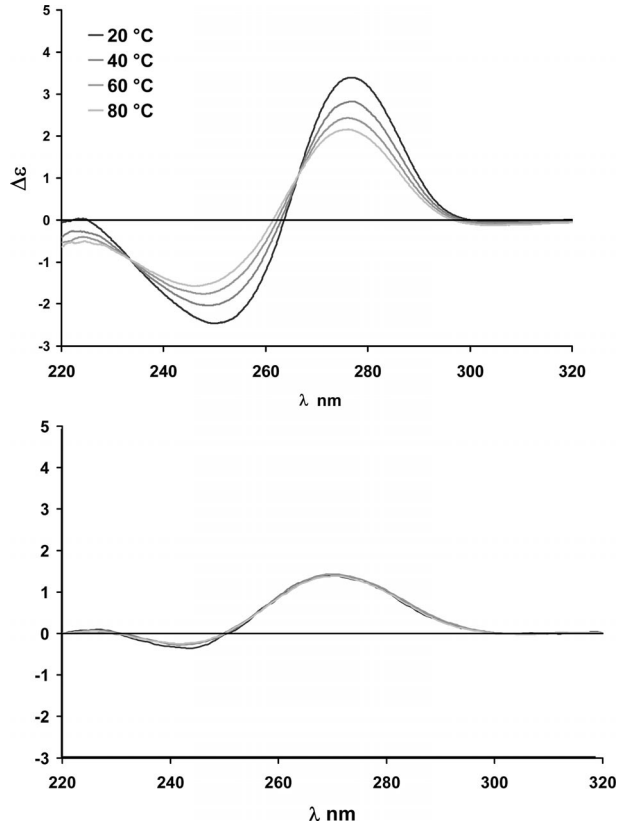


Figure 4. CD spectra of TpU (top) and ($S_{C5'}$,R_P)-α,β-D-CNA TU **22** (bottom) in 10 mM sodium phosphate (pH 7.0) at 80, 60, 40 and 20 °C.

To gain information on the conformational behaviour of this 2′-deoxy-*ribo*/*ribo*-α,β-D-CNA TU in solution, the 2′-*O*- and 3′-*O*-*tert*-butyldimethylsilyl protecting groups were removed with fluoride ion to give **22**, which was analysed by circular dichroism and ^{1}H and ^{31}P NMR (Figure 4 and Table 1).

To evaluate the relative positions of the nucleobases in this constrained dinucleotide, CD spectra were recorded in phosphate buffer (pH 7.0) at 20, 40, 60 and 80 °C and compared with those of the corresponding unmodified thymidine/uridine dinucleotide (denoted as TpU in Figure 4). As previously observed for the α,β-D-CNA TT analogue,[20] the striking features of the CD spectra of α,β-D-CNA TU are the temperature independence and the low intensity of the positive Cotton effect band at around 270 nm, whereas TpU shows variations due to base-stacking disruption with increasing temperature. With the *α* torsional angle locked into the non-canonical *gauche*(+) conformation, the rigidity of the dioxaphosphorinane structure does not allow any base stacking in α,β-D-CNA TU **22**.

To complement this information, the solution-state structure determination in terms of sugar puckering and dioxaphosphorinane conformation was established after careful analysis of the coupling constants depicted in the ^{1}H NMR spectrum of **22** recorded at 500 MHz in deuteriated methanol (Table 1). In contrast to the C-2′ *exo* puckering (North conformation) observed by X-ray analysis for the 2′-deoxyribose moiety of the thymidine of **21**, the small $^2J_{3'H\text{-}4'H}$ coupling constants measured and the values of $^2J_{2'H\text{-}3'H}$ and $^2J_{1'H\text{-}2'H}$ for **22** are consistent with the standard C-2′

Table 1. H–H and H–P coupling constants in the ^{1}H NMR spectra (500 MHz) of *ribo*-α,β-D-CNA.

CNA	Sugar	Coupling constant *J* (Hz)					Sugar pucker[a]
		1',2'	2',3'	3',4'	5',P	7',P	
22 (TU)	up	5.8; 8.4	2.0	3.0	-	-	66% South
	down	4.4	4.8	5.3	<1	n.d.	55 % North
27 (UU)	up	6.0	5.0	3.7	-	-	62% South
	down	3.0	5.3	6.8	<1	1.5; 23.5	69% North
28 (UU)	up	6.1	4.8	3.1	-	-	66% South
	down	4.8	5.0	5.1	<1	1.5; 22.9	52 % North

[a] From the approximation of Altona and Sundaralingam, South (%) = $[J_{1'H,2'H}/(J_{1'H,2'H} + J_{3'H,4'H})] \times 100$.[22]

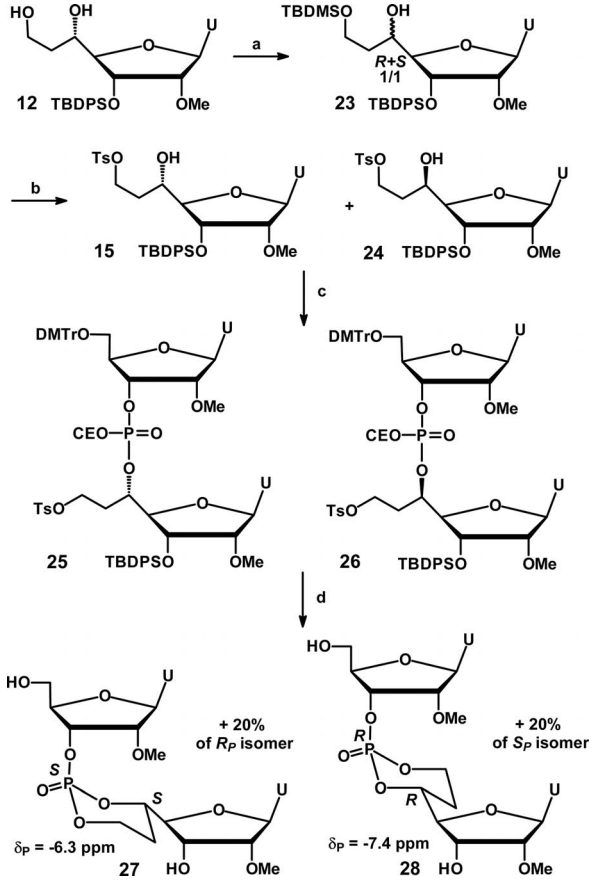
endo conformation (South conformation) previously observed in natural 2′-deoxyribose units.[21] Likewise, the lower uridine ribose sugar adopts the expected C-2′ *exo* conformation (North conformation) according to the Altona–Sundaralingam approximation.[22] On the other hand, the chair conformation of the dioxaphosphorinane ring disclosed in the solid state for **21** is corroborated for **22** by the very small coupling constant exhibited by 5′-H of the lower nucleoside with phosphorus, which is characteristic of an axial position of the proton in this six-membered ring.[23]

Finally, with all these observations in hand, we proposed to synthesise *ribo*/*ribo*-α,β-D-CNA in the 2′-OMe form to avoid any dioxaphosphorinane ring-opening and to enforce the North conformations of the puckered sugar units.

Because we wished to obtain the two main isomers of 2′-*O*-methyl-*ribo*-α,β-D-CNA (featuring either canonical or non-canonical values of α and β) we prepared a mixture of (*S*)-5′-*C*- and (*R*)-5′-*C*-tosyloxyethyl-2′-*O*-methyluridine **15** and **24** (Scheme 5). Starting from diastereopure diol **12**, selective protection of the primary hydroxy function with a *tert*-butyldimethylsilyl group allowed the oxidation of the 5′-hydroxy function with Dess–Martin periodinane[24] immediately followed by the reduction of the corresponding ketone (with $NaBH_4$) to give **23** as a 1:1 mixture of diastereoisomers in 65% overall yield. Removal of the silyl protecting group under mild acidic conditions followed by treatment with tosyl chloride in the presence of pyridine and chloroform provided a 1:1 mixture of **15** and **24** in a moderate 60% yield. Phosphoramidite coupling of separated **15** and **24** with commercially available 2′-*O*-methyluridine phosphoramidite produced the acyclic dinucleotides **25** and **26** as an equimolar mixture of each diastereoisomer (^{31}P NMR: δ = –2.2, –2.3, –2.4 and –2.6 ppm, respectively) in 90% yield after the oxidation step.

2′-OMe-*ribo*-α,β-D-CNA **27** and **28** were isolated from **25** and **26**, respectively, in overall yields of 56% after removal of the protecting groups and dioxaphosphorinane ring formation. In each case the cyclisation process occurred with a modest diastereoselectivity of 4:1. As observed by ^{31}P NMR, minor isomers were detected at –4.8 and –5.2 ppm, respectively. The major isomers were separated from the minor isomers by silica gel chromatography before the deprotection steps.

The CD spectra of *ribo*-α,β-D-CNA **27** and **28** were recorded in phosphate buffer (pH 7.0) at 20, 40, 60 and 80 °C (Figure 5). As expected, the two diastereoisomers exhibit striking different features. Although *ribo*-α,β-D-CNA **28** shows a temperature dependence and a high intensity of the positive Cotton effect at around 270 nm, its diastereoisomer **27** exhibits neither temperature dependence nor a high intensity of the same band. This difference in behaviour is related to the relative positions of the two nucleobase moieties. Therefore it is clear that in the *ribo*-α,β-D-CNA **28** the



Scheme 5. Synthesis of 2′-OMe-*ribo*-α,β-D-CNA UU. Reagents: a) i. TBDMSCl, Py, 90%; ii. Dess–Martin periodinane, Py, DCM, then $NaBH_4$, 72%; b) i. PTSA, MeOH, 85%; ii. TsCl, Py, $CHCl_3$, 60%; c) 2′-OMe-uridine phosphoramidite, tetrazole, CH_3CN then I_2/H_2O/coll, 70%; d) i. K_2CO_3, DMF, 80%; ii. TBAF, THF, then 3% TFA/CH_2Cl_2, 70%.

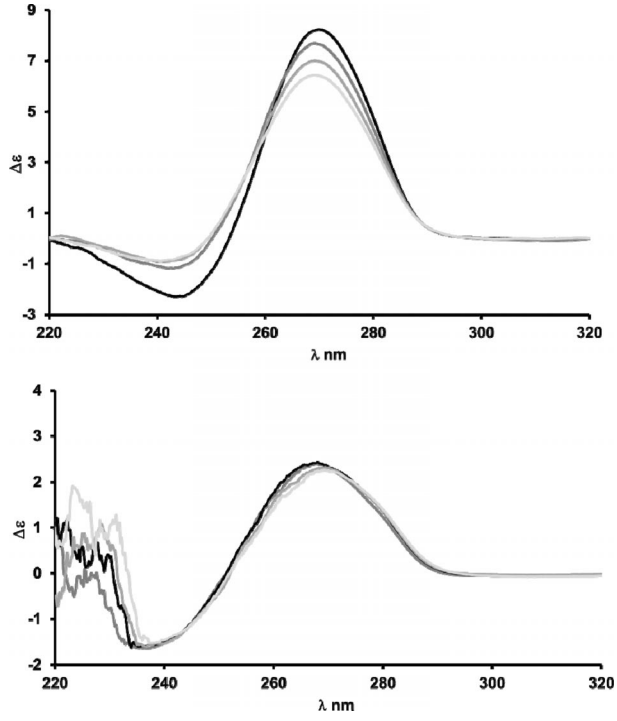


Figure 5. CD spectra of ($R_{C5'}$,R_P)-α,β-D-CNA **28** (top) and ($S_{C5'}$,S_P)-α,β-D-CNA **27** (bottom) in 10 mM sodium phosphate (pH 7.0) at 80, 60, 40 and 20 °C.

torsional constraints allow for base stacking whereas in **27** it is avoided. Thus, circular dichroism is efficient for easily distinguishing and assigning the relative structures of the two diastereoisomers.

The furanose and dioxaphosphorinane solution-state structures of **27** and **28** were determined by means of ^{1}H and ^{31}P NMR spectroscopy in CD_3OD (Table 1). The chair conformation of the dioxaphosphorinane structure of **27** and **28** was clearly established on the basis of the ^{1}H NMR spectra, with the observation of small and large $^3J_{H,P}$ coupling constants between the 7′-H proton and phosphorus, which are characteristic of the axial ($^3J_{Hax\text{-}P} \approx 2$ Hz) and equatorial positions ($^3J_{Heq\text{-}P} \approx 22$ Hz) of these protons.[23] The small $^3J_{H\text{-}P}$ coupling constant between the 5′-H protons and phosphorus (<1 Hz) in both compounds is also consistent with an axial position of these protons in the dioxaphosphorinane ring. Therefore, together with the CD results, it can be concluded that **27** is the ($R_{C5'}$,R_P)-*ribo*-α,β-D-CNA featuring canonical values *gauche*(–)/*trans* for *α* and *β*, and **28** is the ($S_{C5'}$,S_P)-*ribo*-α,β-D-CNA featuring non-canonical values *gauche*(+)/*trans* for *α* and *β*.

Examination of the sugar ring H–H coupling constants allowed the assignment of the puckering of the 2′-OMe ribose moieties of **27** and **28** (Table 1). In each case the upper ribose residue features small $J_{3'H\text{-}4'H}$ (ca. 3 Hz) and rather large $J_{1'H\text{-}2'H}$ (ca. 6 Hz) values close to those found in the standard sugar C-2′ *endo* conformation[21] and similar to those of the 2′-deoxyribose of **22**. On the other hand, the lower units behave as regular ribose units with a preferred C-2′ *exo* conformation that is even strengthened for the dinucleotide **28** exhibiting canonical constraints. Therefore it can be concluded that these ribose dinucleotides mainly present a South/North junction in solution. The neutral internucleotidic linkage induces a more favourable South conformation even for 2′-OMe ribose.[25] Similar observations have been reported in the case of macrocyclic phosphotriester-linked diuridines.[26]

Conclusions

We have synthesised constrained *ribo* dinucleotides with a dioxaphosphorinane structure as the internucleotidic linkage that restrains the *α* and *β* torsional angles (α,β-D-CNA) by connection between the C-5′ of the downstream nucleotide to an oxygen of the phosphate through an ethylene chain.

We showed that in the case of a ribose residue at the 5′-top (*ribo*/2′-deoxy-*ribo*-α,β-D-CNA UT), the 2′-hydroxy function must be protected to avoid a transesterification process due to a highly favourable in-line attack conformation imposed by the cyclic phosphotriester moiety.

Structural analysis, including X-ray crystallography and NMR spectroscopy, allowed us to determine that 1) the Mukaiyama aldol condensation on uridine aldehyde provides an *S*-configured C-5′, 2) the dioxaphosphorinane linkage adopts a true chair conformation in major diastereoisomers of 2′-deoxy-*ribo*/*ribo*- and *ribo*/*ribo*-α,β-D-CNA, 3) due to the neutral internucleotidic linkage, the 5′-top nucleotides adopt a C-2′ *endo* (South) conformation in solution but a C-2′ *exo* pucker can be observed in the solid state for a 2′-deoxyribose and 4) 2′-OMe-*ribo*-α,β-D-CNA can be obtained either with *α* and *β* locked in the *gauche*(–)/*trans* conformation depicted in A- and B-type duplexes or in the atypical *gauche*(+)/*trans* conformation frequently observed in bulged or looped regions of RNA.

A general comparison of the behaviour within oligonucleotides of all α,β-CNAs synthesised by our group[7b,7d,27] is underway and will be presented in a forthcoming paper.

Experimental Section

General: Products were purified by medium-pressure liquid chromatography with a Jobin and Yvon Modoluprep apparatus by using Amicon 6–35 μm or Merck 15 μm silica. NMR spectra were recorded with a Bruker AC 250, Avance 300 or Avance 500 spectrometer (250, 300 or 500 MHz for ^{1}H and 63, 75 or 125 MHz for ^{13}C). Chemical shifts were referenced to the tetramethylsilane. Mass spectra were recorded with a Nermag R10-10 or Perkin–Elmer API 365 spectrometer. All solvents were distilled and dried before use.

The syntheses of compounds **1**, **4**, **7**, **10** and **13** have been described previously,[11] as have compounds **2** and **5**.[15,17]

3′-*O*-(*tert*-Butyldiphenylsilyl)-2′-*O*-methyluridine (3): *tert*-Butyldimethylsilyl chloride (9.63 g, 63.8 mmol) was added to a solution of 2′-*O*-methyluridine (15 g, 58 mmol) in anhydrous pyridine (200 mL) at room temperature. After stirring for 12 h, the reaction mixture was diluted with ethyl acetate (500 mL) and the organic layer washed with a saturated aqueous solution of NH_4Cl, water and brine. After removal of the solvent under reduced pressure, the crude product was dissolved in anhydrous DMF and imidazole (23.72 g, 0.35 mol) and *tert*-butyldimethylsilyl chloride (17.50 g, 63.8 mmol) were added at room temperature. After stirring for 12 h the reaction mixture was diluted with diethyl ether (500 mL) and the organic layer washed three times with water and brine. After removal of the solvent under reduced pressure, the crude product was dissolved in methanol (300 mL) and *p*-toluenesulfonic acid (0.95 g) was added. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added dropwise after 3 h at room temperature. The methanol was evaporated and the residual mixture diluted with ethyl acetate and the organic layer washed with water and brine. The crude oil obtained after removal of the solvent was precipitated in cold petroleum ether to provide **3** as a white powder (27 g, 93% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.50 (m, 1 H, NH), 7.73–760 (m, 5 H, Ph, 6-H), 7.45–7.40 (m, 6 H, Ph), 5.79 (d, J = 3.6 Hz, 1 H, 1′-H), 5.63 (d, J = 8.1 Hz, 1 H, 5-H), 4.24 (t, J = 5.1 Hz, 1 H, 3′-H), 4.12 (m, 1 H, 4′-H), 3.80 (A part of an ABX syst., J = 12.3, 1.5 Hz, 1 H, 5′-H), 3.61 (t, J = 4.2 Hz, 1 H, 2′-H), 3.44 [B part of an AB(X) syst., J = 12.3 Hz, 1 H, 5′-H], 3.37 (s, 3 H, OMe), 1.12 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 150.2, 141.5, 135.8, 133.1, 132.9, 130.2, 129.6, 127.9, 127.8, 127.7, 102.1, 89.7, 84.8, 82.7, 69.8, 60.7, 58.3, 26.9, 19.3 ppm. $C_{26}H_{32}N_2O_6Si$ (496.63): calcd. C 62.87, H 6.49, N 5.64; found C 63.12, H 6.40, N 5.60.

3′-*O*-(*tert*-Butyldiphenylsilyl)-2′-*O*-methyl-5′-oxouridine (6): Dichloroacetic acid (1.15 mL in 28 mL DMSO) was added dropwise to **3** (14.4 g, 29 mmol) and dicyclohexylcarbodiimide (23.8 g, 116 mmol) dissolved in anhydrous DMSO (87 mL) at room temperature. After stirring for 16 h, oxalic acid (10.92 g, 87 mmol) was added portionwise. The reaction mixture was diluted with ethyl

acetate (250 mL) and cooled to 0 °C. After 1 h, the dicyclohexylurea was filtered off and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ and three times with water and brine. After removal of the solvent the residual oil was precipitated in cold petroleum ether to provide **6** as a white powder (13 g, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.39 (d, J = 2.1 Hz, 1 H, 5′-H), 9.28 (s, 1 H, NH), 7.74–7.65 (m, 5 H, Ph, 6-H), 7.47–7.40 (m, 6 H, Ph), 6.02 (d, J = 5.1 Hz, 1 H, 1′-H), 5.75 (d, J = 8.1 Hz, 1 H, 5-H), 4.62 (d, J = 4.2 Hz, 1 H, 3′-H), 4.33 (m, 1 H, 4′-H), 3.53 (t, J = 4.6 Hz, 1 H, 2′-H), 3.29 (s, 3 H, OMe), 1.14 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.2, 163.3, 150.1, 140.6, 135.8, 132.4, 130.4, 128.1, 127.9, 102.8, 894, 87.7, 81.9, 71.3, 58.4, 24.9, 19.3 ppm.

(5′*S*)-2′,3′-*O*-(*tert*-Butyldimethylsilyl)-5′-*C*-(methoxycarbonylmethyl)uridine (8): $BiCl_3$ (82 mg) and ZnI_2 (124 mg) were added to a solution of compound **5** (1.8 g, 3.9 mmol) in anhydrous dichloromethane (11 mL) at room temperature. After stirring for 30 min, silyl ketene (1.92 g, 10.2 mmol) diluted with dichloromethane (3 mL) was added. The black solution turned to a bright-orange colour. After 2 h, the reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of NH_4Cl. The organic layer was collected and washed with water and brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure the crude product was deposited on a silica gel column and eluted with diethyl ether/petroleum ether (7:3): 1.7 g of **8** was recovered as a white foam together with 0.15 g of its C-5′ epimer in 85% yield. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.86 (s, 1 H, NH), 7.93 (d, J = 8.1 Hz, 1 H, 6-H), 5.73 (d, J = 8.2 Hz, 1 H, 5-H), 5.67 (d, J = 6.7 Hz, 1 H, 1′-H), 4.53 (t, J = 4.6 Hz, 1 H, 2′-H), 4.19–4.13 (m, 2 H, 3′-H, 5′-H), 3.92–3.90 (m, 2 H, 4′-H, OH), 3.73 (s, 3 H, MeO), 2.83–2.50 [AB part of AB(X) syst., J = 17.0, 9.7, 3.3 Hz, 2 H, 6′-H], 0.89, 0.87 (2 s, 18 H, *t*Bu), 0.11, 0.10, 0.09, 0.05 (4 s, 12 H, $SiMe_2$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.5, 163.6, 150.5, 141.7, 102.1, 96.1, 91.2, 74.5, 72.0, 66.6, 52.1, 36.0, 25.8, 18.0, –4.6 ppm. $C_{24}H_{44}N_2O_8Si_2$ (544.79): calcd. C 52.91, H 8.14, N 5.14; found C 52.63, H 8.17, N 5.01.

(5′*S*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-5′-*C*-(methoxycarbonylmethyl)-2′-*O*-methyluridine (9): The same procedure as for **8** was followed starting from **6** (6.0 g, 12.9 mmol); **9** (6.2 g, 90% yield) was isolated after precipitation in petroleum ether. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.58 (s, 1 H, NH), 7.87 (d, J = 8.1 Hz, 1 H, 6-H),7.73–7.40 (m, 10 H, Ph), 5.91 (d, J = 3.3 Hz, 1 H, 1′-H), 5.63 (dd, J = 8.1, 2.1 Hz, 1 H, 5-H), 4.28 (t, J = 5.2 Hz, 1 H, 4′-H), 3.97 (d, J = 6. 0 Hz, 1 H, 3′-H), 3.92 (m, 1 H, 5′-H), 3.71 (s, 3 H, OMe), 3.44 (dd, J = 4.8, 3.6 Hz, 1 H, 2′-H), 3.34 (s, 3 H, OMe), 2.71, 2.43 [AB part of AB(X) syst., J = 16.8, 9.9, 3.0 Hz, 2 H, 6′-H], 1.11 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 163.7, 150.3, 140.8, 135.9, 135.8, 133.0, 130.2, 130.1, 127.9, 127.8, 102.0, 88.0, 85.6, 83.0, 70.5, 65.9, 58.1, 52.0, 38.0, 26.9, 19.3 ppm. $C_{29}H_{36}N_2O_8Si$ (568.69): calcd. C 61.25, H 6.38, N 4.93; found C 59.88, H 6.42, N 4.77.

(5′*S*)-2′,3′-*O*-(*tert*-Butyldimethylsilyl)-5′-*C*-(hydroxyethyl)uridine (11): Sodium borohydride (416 mg, 11.0 mmol) was added to compound **8** (1.0 g; 1.83 mmol) dissolved in ethanol (10 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for 12 h. After addition of a saturated aqueous solution of NH_4Cl (30 mL), ethanol was removed under reduced pressure. The residue was extracted with ethyl acetate and the organic layer washed with water and brine and dried with $MgSO_4$. The solvent was removed in vacuo and compound **11** was obtained as a white foam (900 mg, 95% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.41 (s, 1 H, NH), 7.82 (d, J = 8.1 Hz, 1 H, 6-H), 5.73 (dd, J = 8.1, 2.3 Hz, 1 H, 5-H), 5.56 (d, J = 5.4 Hz, 1 H, 1′-H), 4.48 (t, J = 4.8 Hz, 1 H, 3′-H), 4.17–4.11 (m, 2 H, 2′-H, 4′-H), 3.98–3.90 (2 H, 5′-H, 7′-H), 1.68 (m, 2 H, 6′-H), 0.91, 0.88 (2 s, 18 H, *t*Bu), 009, 008, 006, 003 (4 s, 12 H, $SiMe_2$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.9, 150.7, 142.9, 102.1, 92.4, 88.3, 74.0, 72.5, 69.9, 61.2, 35.6, 25.9, 18.1, –4.5 ppm. $C_{23}H_{44}N_2O_7Si_2$ (516.78): calcd. C 53.46, H 8.58, N 5.42; found C 53.37, H 8.42, N 5.47.

(5′*S*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-5′-*C*-(hydroxyethyl)-2′-*O*-methyluridine (12): The same procedure as followed for **11**, starting from **9** (1.0 g, 1.76 mmol); **12** (0.9 g, 95% yield) was isolated as a white foam. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.91 (s, 1 H, NH), 7.82 (d, J = 8.1 Hz, 1 H, 6-H), 7.74–7.40 (m, 10 H, Ph), 5.82 (d, J = 3.9 Hz, 1 H, 1′-H), 5.64 (dd, J = 8.1, 2.1 Hz, 1 H, 5-H), 4.28 (t, J = 5.0 Hz, 1 H, 3′-H), 3.96 (dd, J = 5.1, 1.5 Hz, 1 H, 4′-H), 3.83–3.60 (m, 5 H, OH, 7′-H, 5′-H, 2′-H), 3.33 (s, 3 H, OMe), 1.83 (m, 1 H, 6′-H), 1.55 (m, 1 H, 6′-H), 1.12 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.2, 150.1, 141.7, 135.8, 133.2, 132.9, 130.2, 130.1, 127.9, 127.8, 102.1, 89.4, 87.3, 70.9, 69.5, 61.4, 58.2, 35.4, 26.9, 19.3 ppm. $C_{28}H_{36}N_2O_7Si$ (540.68): calcd. C 62.20, H 6.71, N 5.18; found C 62.10, H 6.77, N 5.02.

(5′*S*)-2′,3′-*O*-(*tert*-Butyldimethylsilyl)-5′-*C*-(tosyloxyethyl)uridine (14): Tosyl chloride (442 mg, 2.3 mmol) was added to compound **11** (0.8 g, 1.55 mmol) dissolved in anhydrous pyridine (1.4 mL) and chloroform (5 mL) at 0 °C. Stirring was maintained for 12 h and the reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of NH_4Cl. The organic layer was collected and washed with water and brine and dried with $MgSO_4$. After removal of the solvent under reduce pressure, the crude product was deposited on a silica gel column and eluted with ethyl acetate/dichloromethane (1:3). Compound **14** was recovered as a white foam (0.89 g, 86% yield). ^{1}H NMR (250 MHz, $CDCL_3$): δ = 8.35 (s, 1 H, NH), 7.80 (d, J = 8.0 Hz, 2 H, Ph), 7.60 (d, J = 8.1 Hz, 1 H, 6-H), 7.35 (d, J = 8.0 Hz, 2 H, Ph), 5.73 (dd, J = 8.1, 2.3 Hz, 1 H, 5-H), 5.43 (d, J = 5.8 Hz, 1 H, 1′-H), 4.55 (dd, J = 5.8, 4.6 Hz, 1 H, 2′-H), 4.16–4.12 (m, 2 H, 3′-H, 4′-H), 3.90–3.85 (m, 2 H, 5′-H, 7′-H), 2.45 (s, 3 H, CH_3 Ts), 1.90 (br. s, 1 H, OH), 1.62 (br. s, 2 H, 6′-H), 0.91, 0.87 (2 s, 18 H, *t*Bu), 0.09, 0.08, 0.02, 0.01 (4 s, 12 H, $SiMe_2$) ppm. ^{13}C NMR (63 MHz, $CDCL_3$): δ = 163.7, 150.5, 145.0, 143.3, 132.3, 130.0, 128.8, 127.9, 126.0, 102.2, 93.4, 88.2, 73.4, 72.8, 67.7, 66.4, 33.5, 25.7, 21.7, 18.1, 1.0, –4.6 ppm. $C_{30}H_{50}N_2O_9SSi_2$ (670.96): calcd. C 53.70, H 7.51, N 4.18; found C 53.95, H 7.49, N 4.11.

(5′*S*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-2′-*O*-methyl-5′-*C*-(tosyloxyethyl)uridine (15): The same procedure was followed as for **14**, starting from **12** (800 mg, 1.48 mmol); **15** (600.0 mg, 58% yield) was isolated as a white foam after column chromatography with ethyl acetate/dichloromethane (1:4) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.60 (s, 1 H, NH), 7.81–7.38 (m, 15 H, Ph, 6-H), 5.74 (d, J = 3.9 Hz, 1 H, 1′-H), 5.62 (dd, J = 8.1, 1.8 Hz, 1 H, 5-H), 4.25–3.99 (m, 3 H, 3′-H, 7′-H), 3.90 (dd, J = 5.4, 1.2 Hz, 1 H, 4′-H), 3.64 (dd, J = 4.8, 3.9 Hz, 1 H, 2′-H), 3.56 (m, 1 H, 5′-H), 3.42 (s, 3 H, OMe), 2.48 (s, 3 H, MeTs), (m, 1 H, 6′-H), 1.13 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 149.9, 145.0, 141.5, 135.8, 132.9, 130.5, 130.2, 130.0, 102.0, 89.7, 86.6, 82.4, 70.7, 65.4, 58.4, 33.2, 26.9, 21.7, 19.2 ppm. $C_{35}H_{42}N_2O_9SSi$ (694.87): calcd. C 60.50, H 6.09, N 5.42; found C 60.58, H 6.06, N 5.39.

[3′-*O*-(*tert*-Butyldiphenylsilyl)-(5′*S*)-5′-*C*-(tosyloxyethyl)-5′-thymidinyl]-2-cyanoethyl-2′-*O*-(*tert*-butyldimethylsilyl)-5′-*O*-dimethoxytrityluridine-2′-phosphate (16): Compound **13** (200 mg, 0.29 mmol), uridine phosphoramidite (0.5 g, 0.58 mmol) and freshly sublimed tetrazole (203 mg, 2.9 mmol) were dissolved in anhydrous acetonitrile (5 mL) and stirred for 120 min at room temperature. After

addition of collidine (157 μL, 1.16 mmol), the phosphite was oxidised with iodine (0.1 M solution in THF/H_2O, 2:1) until the dark-brown colour persisted. The reaction mixture was diluted with ethyl acetate and washed with an aqueous solution of sodium thiosulfate (15%) to remove excess iodine. The organic layer was washed with water and brine and the solvent was removed in vacuo. The crude material was purified by chromatography on silica gel with ethyl acetate as eluent. After evaporation of the solvent compound **16** (mixture of diastereoisomers) was recovered as a white foam (0.3 g, 71% yield). ^{31}P NMR (81 MHz, $CDCl_3$): δ = –2.9, –1.2 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.80–6.80 (m, 29 H, Ph, 6-H), 6.45, 5.95 (2 m, 2 H, 1′-H_U, 1′-H_T), 5.28 (m, 1 H, 7-H_U), 4.81 (m, 1 H, 5′-H), 4.50 (m, 9 H, 3′-H_T, 4′-H, 5′-H, 2′-H_U, 2 CH_2), 3.75, 3.73 (s, 12 H, Me DMTr), 2.71 (m, 2 H, CH_2), 2.44 (s, 3 H, Me Ts), 2.30 (m, 2 H, CH_2), 1.82 (s, 3 H, 7-Me_T), 1.59, 1.24 (2 m, 4 H, 2 CH_2), 1.04, 0.89 (2 s, 18 H, *t*Bu), 0.14, 0.05 (2 s, 6 H, Me) ppm. $C_{74}H_{88}N_5O_{18}PSSi_2$ (1454.74): calcd. C 61.10, H 6.10, N 4.81; found C 61.58, H 6.02, N 4.85.

2′-*O*-(*tert*-Butyldimethylsilyl)-3′-*O*-(*tert*-butyldiphenylsilyl)-5′-*O*-dimethoxytrityl-α,β-D-CNA UT (17): K_2CO_3 (180 mg, 1.24 mmol) was added to a solution of **16** (0.45 g, 0.31 mmol) in anhydrous DMF (7 mL). After 4 h at room temperature the reaction mixture was diluted with ethyl acetate (100 mL) and washed three times with water (3 × 20 mL) and once with brine. The organic layer was dried with $MgSO_4$ and the solvent was removed in vacuo. The cyclic phosphotriester **17** was recovered as a white foam (0.35 g, 92% yield). ^{31}P NMR (81 MHz, $CDCl_3$): δ = –8.5 ppm. ^{1}H NMR (250 MHz, $CDCl_3$): : δ = 9.10, 8.77 (s, 2 H, NH), 7.71 (d, J = 8.1 Hz, 1 H, 6-H_U), 7.60–7.14 (m, 20 H, Ph, 6-H_T), 6.59 (dd, J = 9.4, 5.4 Hz, 1 H, 1′-H_T), 6.14 (d, J = 7.8 Hz, 1 H, 1′-H_U), 5.25 (d, J = 8.1 Hz, 1 H, 7-H_U), 4.95 (dd, J = 4.8, $J_{H\text{-}P}$ = 8.0 Hz, 1 H, 3′-H_U), 4.50 (dd, J = 7.8, 4.8 Hz, 1 H, 2′-H_U), 4.25 (m, 1 H, 3′-H_T), 4.19 (m, $J_{H\text{-}P}$ = 20.0, 2.5 Hz, 2 H, 7′-H_T), 3.89 (m, 1 H, 4′-H_U), 3.69 (m, $J_{H\text{-}P}$ = 6.0 Hz, 1 H, 4′-H_T), 3.34 (m, 3 H, 5′-H_T, 5′-H_U), 2.24 (m, J = 13.3, 5.8, 5.6 Hz, 1 H, 2′-H_T), 2.15 (m, 1 H, 6′-H_T), 1.90 (s, 3 H, 7-H_T), 1.89 (m, 1 H, 2′-H_T), 1.30 (m, 1 H, 6′-H_T), 0.84, 0.85 (s, 18 H, *t*Bu), 0.08, 0.03 (s, 6 H, Me) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 163.8, 162.9, 159.1, 159.0, 150.9, 150.7, 144.0, 135.9–127.6, 113.6, 113.3, 112.4, 102.1, 88.5, 88.0, 86.2, 85.4, 84.8, 83.8, 79.5, 74.8, 67.5, 63.5, 55.5, 40.1, 27.0, 25.7, 19.1, 18.2, 12.6, 0.4, 0.1 ppm. $C_{64}H_{77}N_4O_{15}PSi_2$ (1229.47): calcd. C 62.52, H 6.31, N 4.56; found C 61.99, H 6.25, N 4.52.

2′,3′-*O*-(*tert*-Butyldimethylsilyl)-(5′*S*)-5′-*C*-(tosyloxyethyl)-5′-uridinyl-(2-cyanoethyl)-5′-*O*-dimethoxytritylthymidine-2′-phosphate (20): Following the same procedure as for **16**, starting from **14** (450 mg, 6.7 mmol), **20** (613.0 mg, 70% yield) was isolated as a 1:1 mixture of diastereoisomers. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.88 (2 br. s, 4 H, NH), 7.79–7.71 (m, 2 H, 6-H), 7.52–7.22 (m, 11 H, Ph), 6.85–6.80 (m, 6 H, Ph), 6.45 (m, 2 H, 1′-H), 5.77 (m, 2 H, 5′-H), 4.28–4.11 (m, 15 H, 2′-H, 3′-H, 4′-H, 5′-H, CH_2), 3.78 (s, 6 H, Me DMTr), 2.43 (s, 3 H, Me OTs), 1.64–1.24 (m, 6 H), 0.88, 0.85 (2 s, 18 H, *t*Bu), 0.08, 0.07, 0.05, 0.02 (4 s, 12 H, $SiMe_2$) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = –2.6, –2.4 ppm. $C_{64}H_{84}N_5O_{18}PSSi_2$ (1330.59): calcd. C 57.77, H 6.36, N 5.26; found C 57.52, H 6.26, N 5.44.

2′,3′-*O*-(*tert*-Butyldimethylsilyl)-α,β-D-CNA TU (21): K_2CO_3 (130 mg, 0.9 mmol) was added to a solution of **20** (0.3 g, 0.22 mmol) in anhydrous DMF (5 mL). After 4 h at room temperature the reaction mixture was diluted with ethyl acetate (800 mL) and washed three times with water (3 × 20 mL) and once with brine. The organic layer was dried with $MgSO_4$ and the solvent removed in vacuo. After silica gel chromatography (AcOEt/CH_2Cl_2, 1:1) the cyclic phosphotriester **21** was recovered as a white foam (0.193 g, 80% yield) along with the slower-eluted phosphorus epimer (δ_P = –3.2 ppm, 37 mg, 15%). The major isomer was treated with TFA (3% in CH_2Cl_2, 10 mL). After 15 min the red solution was evaporated to dryness. The crude material was dissolved with THF and submitted to silica gel chromatography. It was first eluted with ethyl acetate to remove the dimethoxytrityl residue and then with 20% methanol in ethyl acetate to give **21** as a white foam after evaporation of the solvent (120 mg, 85% yield). ^{31}P NMR (100 MHz, $CDCl_3$): δ = –8.8 ppm. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.95, 9.57 (s, 2 H, NH), 7.59 (m, 1 H, 6-H_T), 7.35 (d, J = 8.2 Hz, 1 H, 6-H_U), 6.38 (dd, J = 8.0, 6.0 Hz, 1 H, 1′-H_T), 5.82 (dd, J = 8.0, 2.0 Hz, 1 H, 5-H_U), 5.49 (d, J = 6.4 Hz, 1 H, 1'-H_U), 5.21 (tdd, J = 6.2, 2.3, $J_{H\text{-}P}$ = 6.0 Hz, 1 H, 3′-H_T), 4.79 (ddd, J = 11.3, 6.0, 2.3, $J_{H\text{-}P}$ < 1.0 Hz, 1 H, 5′-H_U), 4.75 (dd, J = 6.2, 4.5 Hz, 1 H, 2′-H_U), 4.54–4.43 (m, 2 H, 7′-H_U), 4.35 (br. d, J = 8.0, 6.0 Hz, 1 H, 4′-H_T), 4.28 (dd, J = 4.3, 2.0 Hz, 1 H, 3′-H_U), 3.99–3.91 (m, 3 H, 4′-H_U, 5′-H_T), 2.60, 2.44 [AB part of an ABX(Y) syst., J = 14.0, 5.8, 2.0, 8.0, 6.0 Hz, 2 H, 2′-H_T], 2.11 (m, 1 H, 6′-H_U), 2.00 (m, 1 H, 6′-H_U), 0.94 (s, 9 H, *t*Bu), 0.87 (s, 9 H, *t*Bu), 0.16, 0.14, 0.07, 0.01 (s, 12 H, Me) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.0, 163.5, 150.6, 142.9, 136.3, 111.5, 102.7, 93.6, 86.5, 86.4, 85.6, 79.5, 79.4, 78.0, 72.1, 71.7, 68.5, 62.1, 38.5, 29.7, 28.0, 25.8, 18.0, 12.6, –4.4, –4.5, –4.6 ppm. $C_{33}H_{55}N_4O_{13}PSi_2$ (802.96): calcd. C 49.36, H 6.90, N 6.98; found C 48.92, H 6.75, N 6.70.

α,β-D-CNA TU (22): TBAF (1 M in THF, 136 μL) was added to **21** (50 mg, 0.06 mmol) in anhydrous THF (1 mL) at 0 °C. After stirring for 2 h at room temperature, THF was removed under reduced pressure and the crude was submitted to silica gel chromatography first eluting with ethyl acetate and then with 10% methanol in ethyl acetate to give **22** (28 mg, 79% yield). ^{31}P NMR (81 MHz, CD_3OD): δ = –8.6 ppm. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.79 (m, 1 H, 6-H_T), 7.72 (d, J = 8.1 Hz, 1 H, 6-H_U), 6.34 (dd, J = 8.4, 5.8 Hz, 1 H, 1′-H_T), 5.94 (d, J = 4.4 Hz, 1 H, 1′-H_U), 5.76 (d, J = 8.1 Hz, 1 H, 7-H_U), 5.11 (br. q, J = 6.0, 2.1 Hz, 1 H, 3′-H_T), 4.84 (m, J = 11.7, 2.3, $J_{H\text{-}P}$ < 1.0 Hz, 1 H, 5′-H_U), 4.55–4.50 (m, 2 H, 7′-H_U), 4.26 (t, J = 2.8 Hz, 1 H, 4′-H_T), 4.23 (d, J = 5.3 Hz, 1 H, 3′-H_U), 4.16 (d, J = 4.8 Hz, 1 H, 2′-H_U), 4.05 (m, J = 5.3, 2.4, $J_{H\text{-}P}$ = 4.6 Hz, 1 H, 4′-H_U), 3.81 (d, J = 3.0 Hz, 1 H, 5′-H_T), 2.57 (m, J = 14.3, 8.4, $J_{H\text{-}P}$ = 1.2 Hz, 1 H, 2′-H_T), 2.43 (m, J = 14.3, 5.8 Hz, 1 H, 2′-H_T), 2.38 (m, 1 H, 6′-H_U), 1.88 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 152.4, 141.9, 137.8, 111.9, 111.4, 108.0, 103.1, 90.8, 87.0, 86.0, 85.4, 79.8, 75.0, 71.1, 62.5, 39.4, 28.8, 12.4, 9.6 ppm. $C_{21}H_{27}N_4O_{13}P$ (574.43): calcd. C 43.91, H 4.74, N 9.75; found C 43.88, H 4.78, N 10.02.

3′-*O*-(*tert*-Butyldiphenylsilyl)-5′-*C*-(*tert*-butyldimethylsilyloxyethyl)-2′-*O*-methyluridine (23): *tert*-Butyldimethylsilyl chloride (0.12 g, 0.81 mmol) was added to a solution of **12** (0.33 g, 0.61 mmol) in anhydrous pyridine (5 mL) at room temperature. After stirring for 12 h, the reaction mixture was diluted with ethyl acetate (50 mL) and the organic layer was washed with a saturated aqueous solution of NH_4Cl, water and brine. After removal of the solvent under reduced pressure, the crude product was dissolved in anhydrous dichloromethane (5 mL) and pyridine (40 μL) and Dess–Martin periodinane (0.517 mg, 1.22 mmol) was added. After 12 h at room temperature ethanol (5 mL) and $NaBH_4$ (140 mg, 3.66 mmol) were added at 0 °C. After stirring for 20 h at room temperature the reaction mixture was diluted with ethyl acetate (100 mL) and washed with a saturated aqueous solution of NH_4Cl, water and brine. After silica gel chromatography with ethyl acetate/dichloromethane (1:4) as eluent, **23** (0.3 g, 75% yield) was isolated as a white foam as a 1:1 mixture of C-5′ epimers. Data for the 5′*S* epimer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.67 (s, 1 H, NH), 8.05 (d, J = 8.1 Hz, 1

H, 6-H), 7.75–7.39 (m, 10 H, Ph), 5.97 (d, J = 3.6 Hz, 1 H, 1′-H), 5.60 (dd, J = 8.1, 1.5 Hz, 1 H, 5-H), 4.31 (t, J = 5.0 Hz, 1 H, 3′-H), 3.93 (m, 2 H, 7′-H, 4′-H), 3.72 (m, 2 H, 7′-H, 5′-H), 3.36 (dd, J = 4.8, 3.8 Hz, 1 H, 2′-H), 3.31 (s, 3 H, OMe), 1.92 (m, 1 H, 6′-H), 1.53 (m, 1 H, 6′-H), 1.12 (s, 9 H, *t*Bu), 0.93 (s, 9 H, *t*Bu), 0.12, 0.10 (s, 6 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 150.0, 140.8, 135.9, 135.8, 130.1, 130.0, 127.7, 101.8, 87.4, 86.9, 83.2, 70.7, 70.2, 62.8, 58.0, 35.0, 26.9, 25.8, 19.3, 18.01, –5.5 ppm. MS (ESI): m/z = 667.8 [M + Na]$^+$. $C_{34}H_{52}N_2O_7Si_2$ (654.95): calcd. C 62.35, H 7.69, N 4.28; found C 61.85, H 7.59, N 4.52.

(5′*R*)-3′-*O*-(*tert*-Butyldiphenylsilyl)-2′-*O*-methyl-5′-*C*-(tosyloxyethyl)uridine (24): *p*-Toluenesulfonic acid (50 mg) was added to a mixture of **23** (0.3 g, 0.46 mmol) in MeOH (5 mL). A saturated aqueous solution of $NaHCO_3$ (10 mL) was added dropwise after 3 h at room temperature. The methanol was evaporated and the residual mixture diluted with ethyl acetate and washed with water and brine. After removal of the solvent, the residual oil was precipitated into cold petroleum ether to provide a white powder (210 mg, 85% yield). This powder was dissolved in anhydrous pyridine (0.35 mL) and chloroform (1.5 mL) and tosyl chloride (111 mg, 0.58 mmol) was added at 0 °C. Stirring was maintained for 12 h and the reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous solution of NH_4Cl. The organic layer was collected and washed with water, brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was deposited on a silica gel column and eluted with ethyl acetate/dichloromethane (1:3). After two separation processes, compounds **15** and **24** were isolated from each other and recovered as white foam (79 and 83 mg, 60% combined yield). Data for **24**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (s, 1 H, NH), 7.78–7.35 (m, 15 H, Ph, 6-H), 5.77 (dd, J = 7.8, 2.1 Hz, 1 H, 5-H), 5.61 (d, J = 6.3 Hz, 1 H, 1′-H), 4.32 (dd, J = 4.8, 2.4 Hz, 1 H, 3′-H), 4.09–3.89 (m, 4 H, OH, 4′-H, 7′-H), 3.79 (qd, J = 10.8, 2.7 Hz, 1 H, 5′-H), 3.57 (br. d, J = 2.4 Hz, 1 H, 2′-H), 3.18 (s, 3 H, OMe), 2.47 (s, 3 H, MeTs), 1.62 (m, 1 H, 6′-H), 1.10 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.5, 150.1, 143.2, 136.0, 135.9, 132.9, 132.8, 129.9, 128.0, 102.7, 92.0, 89.2, 81.0, 70.0, 67.5, 67.2, 58.3, 31.3, 26.9, 21.7, 19.4 ppm. $C_{35}H_{42}N_2O_9SSi$ (694.87): calcd. C 60.50, H 6.09, N 5.42; found C 60.35, H 6.10, N 5.37.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-*O*-methyl-*C*-(tosyloxyethyl)-5′-uridinyl-2-cyanoethyl-2′-*O*-methyl-5′-*O*-dimethoxytrityluridine-2′-phosphate (25 and 26): Following the same procedure as for **16**, starting from a 1:1 mixture of **15** and **24** (115 mg, 0.17 mmol), a 1:1 mixture of diastereoisomers **25** and **26** (158.0 mg, 70% yield) was isolated after silica gel chromatography eluted with ethyl acetate/dichloromethane (9:1). ^{31}P NMR (100 MHz, C_6D_6): δ = –2.6, –2.4, –2.3, –2.2 ppm. $C_{66}H_{72}N_4O_{19}PSSi$ (1370.50): calcd. C 60.47, H 5.59, N 5.11; found C 60.58, H 5.63, N 5.02.

($S_{C5'}$,S_P)-2′,2′-*O*-Methyl-α,β-D-CNA UU (27): The same procedure as for **21**/**22** was followed. ^{31}P NMR (100 MHz, CD_3OD): δ = –6.3 ppm. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.07 (d, J = 8.5 Hz, 1 H, 5a-H), 7.78 (d, J = 8.0 Hz, 1 H, 5b-H), 6.08 (d, J = 6.0 Hz, 1 H, 1′a-H), 6.00 (d, J = 3.0 Hz, 1 H, 1′b-H), 5.77 (d, J = 8.0 Hz, 1 H, 6b-H), 5.76 (d, J = 8.5 Hz, 1 H, 6a-H), 5.05 (m, J = 4.8, 3.7, $J_{H\text{-}P}$ = 7.4 Hz, 1 H, 3′a-H), 4.90 (m, J = 11.0, 4.0, 2.2, $J_{H\text{-}P}$ < 1.0 Hz, 1 H, 5′b-H), 4.66 (m, J = 11.0, 4.9, 1.5, $J_{H\text{-}P}$ = 23.5 Hz, 1 H, 7′b-H), 4.55 (m, J = 13.0, 11.0, 1.8, $J_{H\text{-}P}$ = 1.5 Hz, 1 H, 7′b-H), 4.32 (m, 2 H, 4′a-H, 3′b-H), 4.19 (br. t, J = 6.0, 5.0 Hz, 1 H, 2′a-H), 4.05 (m, J = 6.8, 2.2, $J_{H\text{-}P}$ = 4.6 Hz, 1 H, 4′b-H), 3.84 (m, J = 12.5, 2.8, 2.5 Hz, 2 H, 5′a-H), 3.52, 3.51 (s, 6 H, Me), 2.42 (m, 1 H, 6′b-H), 2.00 (m, 1 H, 6′b-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 164.6, 164.5, 150.9, 150.6, 140.7, 140.1, 101.8, 101.6, 87.6, 86.6, 83.8, 82.9, 79.6, 74.6, 68.7, 68.3, 60.3, 57.7, 57.6, 27.6 ppm. $C_{22}H_{29}N_4O_{14}P$ (604.46): calcd. C 43.72, H 4.84, N 9.27; found C 43.91, H 4.75, N 9.56.

($R_{C5'}$,R_P)-2′,2′-*O*-Methyl-α,β-D-CNA UU (28): ^{31}P NMR (100 MHz, CD_3OD): δ = –7.4 ppm. ^{1}H NMR (500 MHz, CD_3OD): δ = 8.07 (d, J = 8.5 Hz, 1 H, 5a-H), 7.76 (d, J = 8.1 Hz, 1 H, 5b-H), 6.11 (d, J = 6.1 Hz, 1 H, 1′a-H), 5.97 (d, J = 4.8 Hz, 1 H, 1′b-H), 5.76 (d, J = 8.1 Hz, 2 H, 6b-H, 6a-H), 5.05 (m, J = 4.7, 3.1, $J_{H\text{-}P}$ = 7.4 Hz, 1 H, 3′a-H), 5.01 (m, J = 12.0, 3.8, 2.2, $J_{H\text{-}P}$ < 1.0 Hz, 1 H, 5′b-H), 4.58 (m, J = 11.6, 2.2, $J_{H\text{-}P}$ = 22.9 Hz, 1 H, 7′b-H), 4.55 (m, J = 11.6, 5.4, 1.5, $J_{H\text{-}P}$ = 1.5 Hz, 1 H, 7′b-H), 4.46 (t, J = 5.1 Hz, 1 H, 3′b-H), 4.32 (td, J = 2.9, 2.6 Hz, 1 H, 4′a-H), 4.17 (dd, J = 6.0, 4.8 Hz, 1 H, 2′a-H), 4.06 (m, J = 4.7, 4.0, $J_{H\text{-}P}$ = 3.3 Hz, 1 H, 4′b-H), 3.86, 3.82 [AB part of an ABX(Y), J = 12.5, 2.7, 2.4 Hz, 2 H, 5′a-H], 3.52, 3.51 (s, 6 H, Me), 2.30 (m, J = 14.1, 12.2, 5.6, $J_{H\text{-}P}$ < 1 Hz, 1 H, 6′b-H), 2.02 (m, 1 H, 6′b-H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 164.6, 164.5, 150.9, 150.7, 140.7, 140.6, 101.9, 101.7, 87.5, 86.1, 84.7, 84.1, 82.2, 81.8, 79.9, 75.3, 69.0, 67.7, 60.4, 57.9, 57.4, 26.9 ppm. $C_{22}H_{29}N_4O_{14}P$ (604.46): calcd. C 43.72, H 4.84, N 9.27; found C 44.02, H 4.81, N 9.32.

Computational Details: All calculations were performed with the Gaussian 98 set of programs using hybrid density functional methods.[28] The Lee, Yang and Parr correlation functional (B3LYP) was used.[29] A double-ζ plus polarisation valence basis set was employed for each atom including hydrogen.[mod3] The s and p diffuse functions were added for oxygen atoms (ζ_s = 0.108151 and ζ_p = 0.070214). Standard pseudo-potentials developed in Toulouse were used to describe the atomic cores of all non-hydrogen atoms.[30] The structural parameters were produced from full geometry optimisation procedures in the gas phase with no imposed constraints. The harmonic frequencies of these B3LYP optimised structures were calculated to verify that the localised stationary points coincide with energy minima.

Circular Dichroism Studies: These experiments were performed with a Jasco J-815 CD spectrometer equipped with a Peltier controller Jasco PTC-4235/15 at a dinucleotide concentration of 0.1 mM in 10 mM Na_2HPO_4, 100 mM NaCl, 0.1 mM Na_2EDTA buffer, pH 7.00 ± 0.02. Molar extinction coefficients were calculated from those of dinucleotides using the nearest-neighbour approximation method assuming that α,β-D-CNAs have the same molar extinction coefficient as DNA. The dinucleotide concentration was determined from the UV absorbance at high temperature (90 °C). All CD spectra were recorded after stabilisation of the temperature for 10 min and were normalised by subtraction of the background scan with buffer. Taking the known dinucleotide concentration into account, the normalised spectra were converted to show the variation of the molar extinction coefficient ($\Delta\varepsilon$) with wavelength.

Crystal Structure Determination for 21: To determine the structure of compound **21** the selected crystal was mounted on a glass fibre by using perfluoropolyether oil and cooled rapidly to 193 K in a stream of cold N_2. X-ray intensity data were collected with graphite-monochromated Mo-K_α radiation (wavelength = 0.71073 Å) with a Bruker-AXS kappa APEX II Quazar diffractometer by using ϕ and ω scans and a 30-W air-cooled microfocus source (ImS) with focusing multilayer optics at a temperature of 193(2) K. The data were integrated with SAINT[31] and an empirical absorption correction was applied with SADABS.[32] The structure was solved by direct methods (SHELXS-97)[33] and refined against all data by full-matrix least-squares methods on F^2 (SHELXL-97).[34] All non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically

on calculated positions using a riding model with their U_{iso} values constrained to $1.5U_{eq}$ of their pivot atoms for terminal sp^3 carbon atoms and $1.2U_{eq}$ for all other carbon atoms.

$C_{34}H_{58}Cl_3N_4O_{14}PSi_2$, M = 940.34, orthorhombic, space group $P2_12_12_1$, a = 10.4871(2), b = 12.3607(2), c = 39.4965(8) Å, V = 5119.85(16) Å^3, Z = 4, crystal size $0.38 \times 0.30 \times 0.04$ mm^3, 35016 reflections collected (8502 independent, R_{int} = 0.0532), 737 parameters, R_1 [$I > 2\sigma(I)$] = 0.0818, wR_2 (all data) = 0.2509, absolute structure parameter –0.01(17), largest diff. peak and hole 0.923 and –0.409 e Å^{-3}.

CCDC-844478 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.

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