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Diastereoselective Synthesis of Conformationally Restricted Dinucleotides Featuring Canonical and Noncanonical α/β Torsion Angle Combinations (α,β-D-CNA)

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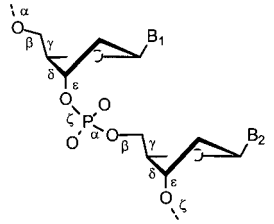
The synthesis of the four possible diastereoisomers of α,β-D-CNA 5′-XT (X = A, T, G and C) building units of nucleic acids, in which the α and β torsional angles are stereocontrolled by a dioxaphosphorinane ring structure (D-CNA family) is described. The crystal structure analysis of the ($R_{C5'}$,S_P)-configured α,β-D-CNA TT dimer demonstrates that the α and β torsional angles are restricted to the canonical {gauche(–),*trans*} conformation typically observed in DNA duplexes.

Introduction

Oligonucleotide analogues have attracted considerable attention over the last two decades due to their potential use in many areas of science including molecular biology, medicinal chemistry, material science and nanotechnology. Because most, if not all, of the expected applications of DNA analogues rely on their ability to form stable and specific helical complexes to a target nucleic acid, much attention has been devoted to the design of synthetic analogues with enhanced binding properties.

According to the concept of preorganization,[1] high affinity and high selectivity should, in principle, be achieved by a single structural modification, which would rigidify a single-stranded oligonucleotide into a shape that more resembles the shape of this strand in its complexed form. With regard to duplex formation, an ideal oligonucleotide analogue should, therefore, have a single-stranded conformational preorganization that fits with the standard A- or B-form helical structures of nucleic acids; that is, it should possess torsion angle values and sugar puckers similar to the values observed in A- or B-form duplexes (Figure 1).



DNA duplex conformation	Torsion angle [°]					
	α	β	γ	δ	ε	ζ
B	–62±15 (g^-)	176±9 (t)	48±11 (g^+)	128±13	–176±11	–95±10
A	–67±17 (g^-)	174±14 (t)	56±14 (g^+)	81±7	–157±12	–71±12

Figure 1. Summary of the average backbone torsion angles α–ζ, derived from natural DNA. Values are from: B. Schneider, S. Neidle, H. M. Berman, *Biopoly* **1997**, *42*, 113–124. The torsion angle ranges are indicated in parentheses for α–γ: gauche(–) = 300 ± 30° (g^-), gauche(+) = 60 ± 30° (g^+) and *trans* = 180 ± 30° (t).

The furanose ring in nucleosides or in single-stranded nucleic acids is well known to have relatively large conformational flexibility.[2] When a nucleic acid forms a duplex (or triplex), however, the conformational freedom is drastically restricted. Thus, one way to efficiently preorganize a single-stranded oligonucleotide for favourable duplex formation is to strongly restrict its furanose unit into either an S-type conformation (C2′-*endo*, B-form duplexes) or an N-type conformation (C3′-*endo*, A-form duplexes). A great number of conformationally restricted oligonucleotides have been produced based on this principle.[3–6] It turned out that constraining the furanose moieties of an oligonu-

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cleotide into the C3′-*endo* (N-type) conformation is indeed a very productive way of improving its duplex- and triplex-forming ability.[7–10]

In contrast, very little attention has been devoted to the preparation of oligonucleotide analogues with a conformationally restricted phosphate linkage. Previous studies involving conformational restriction around the phosphate backbone have been mostly concentrated on the stabilization of nonhelical secondary or tertiary structural elements found especially in RNA.[11,12] For the purpose of constructing covalently constrained nucleic acids (CNA) with specific canonical or noncanonical backbone conformations, we have developed dimeric building units, referred to as D-CNA, in which two or three of the backbone torsion angles α–ζ are part of a dioxaphosphorinane ring structure (Figure 2).[13,14] We recently reported the synthesis of the ($S_{C5'}$,R_P)-configured α,β-D-CNA TT dimer, in which the α and β torsion angles are locked in a noncanonical {gauche(+),*trans*} conformation, which frequently occurs in protein-DNA complexes and in bulged regions of nucleic acids.[13] Herein, we disclose the detailed synthesis and crystal structure of its ($R_{C5'}$,S_P) stereoisomer, in which α and β

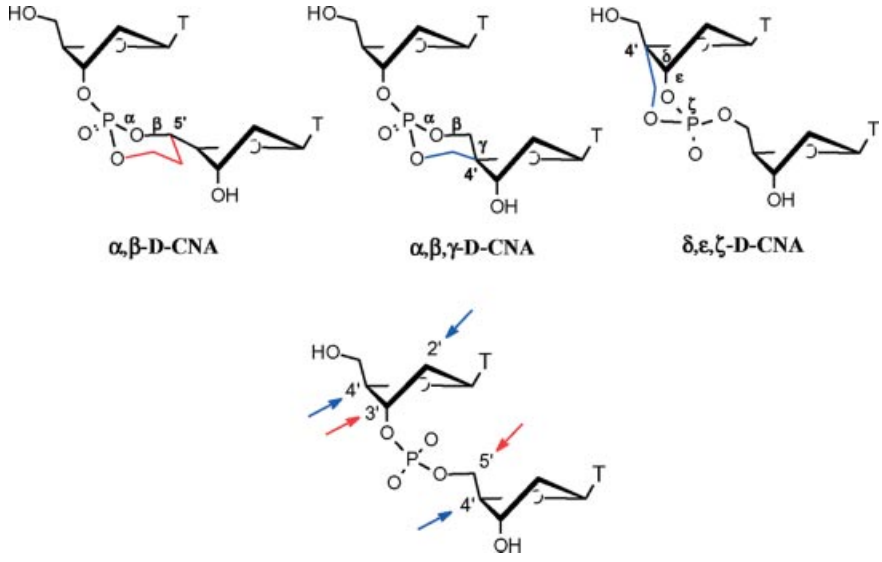


Figure 2. Example of previously described D-CNA dimeric units. D-CNA are oligonucleotides that contain one or more D-CNA dimers, in which a set of backbone torsion angles α–ζ is stereocontrolled to canonical or noncanonical values by a 1,3,2-dioxaphosphorinane ring structure. For a given dinucleotide step, there are fourteen possible [β-D-deoxyribo]-configured D-CNA stereoisomers, which formally result from the introduction of a methylene/ethylene linker between the nonbridging phosphate oxygen atoms and the 2′/4′-carbon atoms (methylene linker, blue arrows) or 3′/5′-carbon atoms (ethylene linker, red arrows).

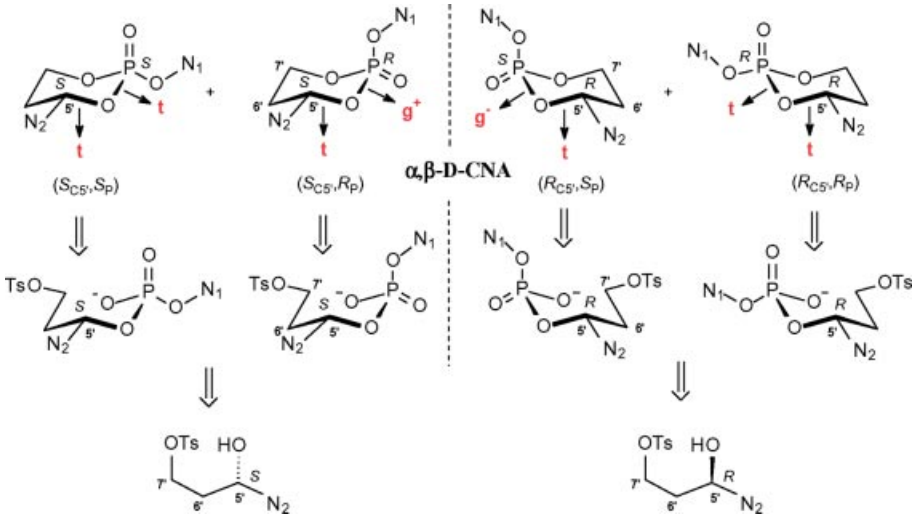


Figure 3. Retrosynthetic pathway for the diastereoselective synthesis of the four possible stereoisomers of α,β-D-CNA dimers. N_1 and N_2 stand for the remaining atomic fragments that define the upper and lower nucleoside units, respectively. The expected gauche(+), gauche(–), or *trans* conformations of α (P–O5′) and β (O–C5′) are indicated for the hypothetical true chair conformations associated with each diastereoisomer.

adopt the canonical {gauche(–),*trans*} conformation found in nucleic acid duplexes. The exceptional binding properties of duplexes involving these two α,β-D-CNA dimers have been reported recently.[15] We also describe the synthesis and solution structure of all possible diastereoisomers derived from the α,β-D-CNA GT, CT and AT dimers.

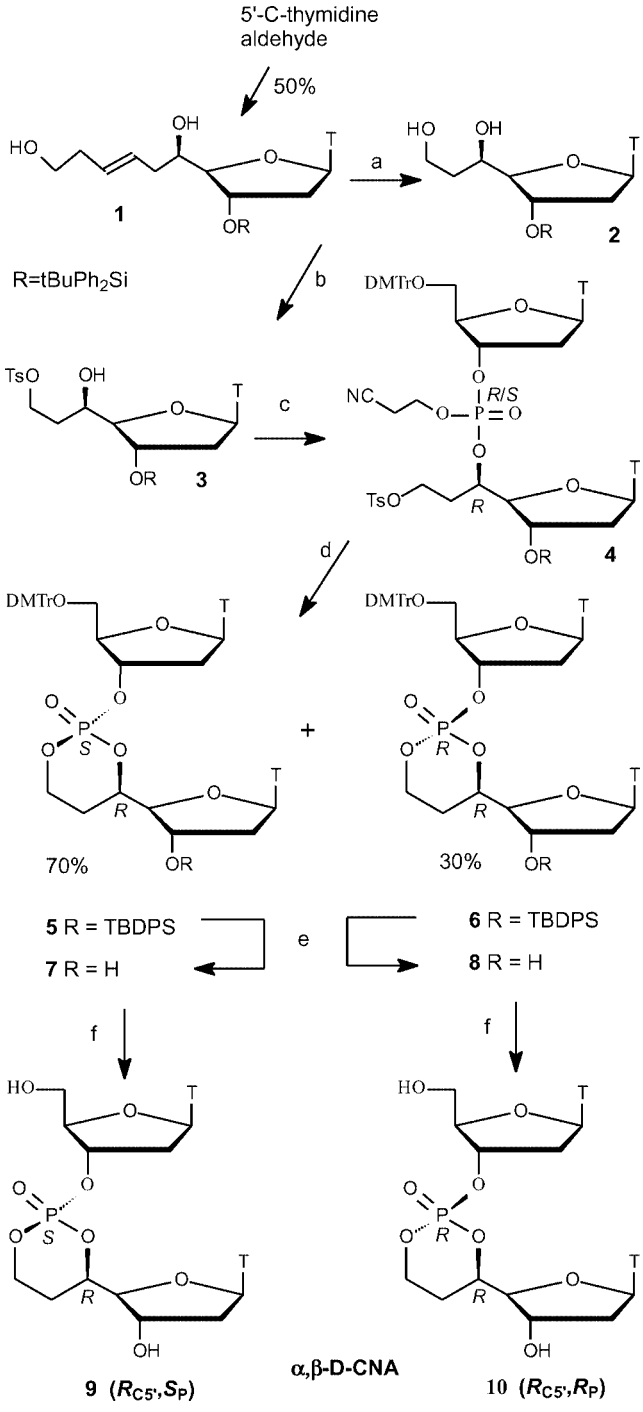
Results and Discussion

Our retrosynthetic analysis for the synthesis of the four possible stereoisomers of a given α,β-D-CNA dinucleotide step is summarized in Figure 3. It is based on the very simple strategy that consists of using both steric and anomeric effects to stereocontrol the cyclization reaction of a dinucleotide precursor in which the pro-(*R*)- and pro-(*S*)-phosphate oxyanions can attack an electrophilic tosyloxy-substituted carbon atom. Among the four possible α,β-D-CNA diastereoisomers, we anticipated that the ($S_{C5'}$,R_P) and ($R_{C5'}$,S_P) isomers with the alkoxy group ON_1 axial (equatorial P=O) and the carbon group N_2 equatorial would be formed preferentially due to the sterically and anomerically favourable *trans* relationship between ON_1 and N_2 in the corresponding six-membered chair conformations. Actually, the cyclization reaction from the (5′*S*)-configured acyclic TT precursor was completely diastereoselective, leading exclusively to the ($S_{C5'}$,R_P)-configured dimer with an {α(g^+),β(t)} conformation.[13] As shown in Figure 3, the key starting material for the preparation of this diastereoisomer is the diastereopure (5′*S*)-*C*-tosyloxyethyl-substituted nucleoside, which is obtained by a Mukaiyama-type aldolisation reaction on the corresponding 5′-*C*-aldehyde nucleoside.[16] Similarly, the preparation of the ($R_{C5'}$,S_P) stereoisomer featuring the canonical {α(g^-),β(t)} conformation requires the preparation of the (5′*R*)-*C*-tosyloxyethyl-substituted nucleoside.

($R_{C5'}$,S_P)- and ($R_{C5'}$,R_P)-Configured α,β-D-CNA TT Dimers

Our synthesis of the (5′*R*)-*C*-(tosyloxyethyl)thymidine **3** involves the preparation of the diastereopure (5′*R*)-*C*-(hydroxyethyl)thymidine **2** (Scheme 1). The latter compound was obtained in 64% combined yield by a three-step oxidative cleavage of the double bond of the available (5′*R*)-*C*-(hydroxypentenyl)thymidine **1**, prepared by a Sakurai allylation reaction of the 5′-*C*-thymidine aldehyde.[17] Selective tosylation of the primary hydroxy group of **2** was achieved in 77% yield by treating **2** with tosyl chloride in the presence of pyridine.[18]

(5′*R*)-*C*-(Tosyloxyethyl)thymidine **3** was then coupled with the commercially available thymidine phosphoramidite according to standard phosphoramidite technology[19] to give two diastereoisomeric dinucleotides **4** in an equimolar ratio. Under the reaction conditions used to release the charged phosphodiester function of **4** (Et_3N, DMF and 90 °C), cyclization occurred in a 90% yield providing a 7:3 diastereoisomeric mixture of the ($R_{C5'}$,S_P) and ($R_{C5'}$,R_P) diastereoisomers **5** and **6**, respectively, as observed by ^{31}P NMR (δ = –9.1 ppm and –5.9 ppm). The cyclization reaction from the (5′*R*)-configured acyclic phosphate precursor (70% *de*) appears, therefore, less diastereoselective than that



Scheme 1. Diastereoselective synthesis of the ($R_{C5'}$,S_P)- and ($R_{C5'}$,R_P)-configured α,β-D-CNA TT dimers. Reagents and conditions: (a) i) OsO_4 cat., *N*-methylmorpholine *N*-oxide, H_2O. ii) $NaIO_4$, MeOH. iii) $NaBH_4$, EtOH, 64% overall yield. (b) TsCl, Pyr, $CHCl_3$, 77%. (c) 5′-*O*-Dimethoxytrityl-3′-*O*-phosphoramidite-thymidine, tetrazole, CH_3CN, then collidine, I_2/H_2O, 93%. (d) Et_3N, DMF, 90 °C, 90%. (e) nBu_4NF, THF, 86–90%. (f) 3% TFA in CH_2Cl_2, 77–85%.

previously observed for the corresponding (5′*S*) isomer (100% *de*).[13] The reason for this difference in diastereoselectivity is presently unclear. Both diastereoisomers **5** and **6** were easily separated at this stage by silica gel chromatography ($\Delta R_f = 0.3$ in AcOEt). Finally, the sequential removal of the protective groups with fluoride ion and trifluoroacetic acid (TFA) provided the final compounds ($R_{C5'}$,S_P)-**9** and ($R_{C5'}$,R_P)-**10** in ca. 21% and 9% overall yields, respectively, from **1**.

The dinucleotide analogues **9** and **10** were fully characterized by elemental analysis and mass spectrometry and by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. The determination of the absolute configuration at the C5′ atom and the newly created asymmetric P centre of both stereoisomers was greatly simplified by the X-ray structure of **9**, identified as the ($R_{C5'}$,S_P) diastereoisomer (Figure 4). This crystal structure gives evidence that the dioxaphosphorinane linkage of the ($R_{C5'}$,S_P)-configured dimer is in a true chair conformation, as expected, with backbone torsion angle values $\delta(N_1)$ = 147.1°, $\delta(N_2)$ = 138.9°, ε = –154.2°, ζ = 176.2°, α = –69.0°, β = –173.9° and γ = 49.0°. The X-ray structure of

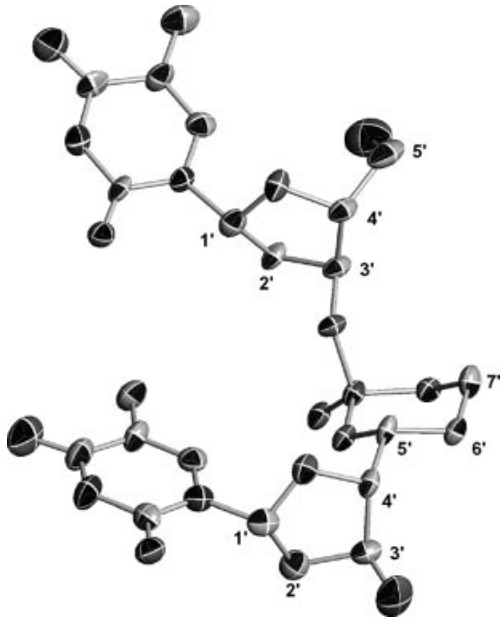


Figure 4. X-ray molecular structure of the ($R_{C5'}$,S_P)-configured α,β-D-CNA TT dimer **9** with the adopted numbering scheme, displaying the chair and C2′-*endo* conformations of the dioxaphosphorinane and sugar subunits. For clarity, hydrogen atoms and cocrystallized solvent molecules are omitted, and thermal ellipsoids are shown at 40% probability.

9 also reveals that both sugar rings are in the C2′-*endo* (south-type) conformation, which is typical of B-DNA, with pseudorotation phase angles of 160° and 159° (Table 1).

The solid-state structure of **9** agrees with the solution-state structure obtained by NMR spectroscopy. The chair conformation of **9** is, like its ($S_{C5'}$,R_P) diastereoisomer,[13] clearly established from the ^{1}H NMR spectra, with no detectable coupling between the 5′-H involved in the dioxaphosphorinane system and P ($^3J_{H5'/P} \approx 0$), which is characteristic of an axial position for this proton.[20] The observation of small (3 Hz) and large (20 Hz) $^3J_{H/P}$ values between the dioxaphosphorinane 7′-H protons and P are also indicative of an axial and an equatorial position of these protons, respectively. In contrast, average values of 10.4 Hz and 12.4 Hz were observed for the $^3J_{H/P}$ values involving the two 7′-H protons of **10**, suggesting that the dioxaphosphorinane structure of this ($R_{C5'}$,R_P)-configured isomer (Figure 3) is in a twist-chair conformation. This "in-between" conformation probably results from the involvement of conflicting steric and anomeric effects in either chair conformation of **10** due to the *cis* relationship between the ON_1 and N_2 groups.

Additional important structural information relative to compounds **9** and **10** resides in the observation of a long-range coupling between the 4′-H proton of the lower sugar unit and P ($^4J_{H4'/P}$ = 2–3 Hz). This coupling is indicative of a typical W-shaped P–O5′–C5′–C4′–H4′ junction (also observed in the crystal structure of **9**), which is consistent with gauche(+) and anticlinal(–) conformations of γ in **9** and **10**, respectively. The W-shaped P–O5′–C5′–C4′–H4′ junction deduced in the case of **10** also suggests that the backbone torsion angles α and β are not significantly affected by the conformational change involved between the true chair and twist-chair forms of **10**. Overall, these NMR spectroscopic data allow us to assign the conformation of the backbone torsion angles α, β, and γ as (α,β,γ) = (g^-,t,g^+) for **9** and (α,β,γ) = (t,t,a^-) for **10**. In addition, the empirical equation established by Lankhorst et al.[21] can be used to determine, from the $J_{H3'/P}$ value (5.8 Hz for **9** and 6.4 Hz for **10**), the value of the torsional angle ε (–160° for **9** and –157° for **10**) and, therefore, the relative position of the upper nucleosides toward the dioxaphosphorinane linkage.

The puckering of the 2′-deoxyribose moieties of **9** and **10** in solution was determined by examination of the sugar ring H/H coupling constants (Table 2). The small $J_{H3'/H4'}$ values measured for **9** and **10** and the values of $J_{H2'/H3'}$ and $J_{H1'/H2'}$ are consistent with the standard C2′-*endo* confor-

Table 1. X-ray crystal values [°] of the glycosyl (χ) and endocyclic (ν_0–ν_4) torsion angles along with the pseudorotation phase angles (P) of both sugar units of the ($R_{C5'}$,S_P)-configured α,β-D-CNA TT dimer **9**.[a]

	χ	ν_0	ν_1	ν_2	ν_3	ν_4	P[b]	Puckering mode[b]
Upper unit (N_1)	–115.9	–20.5	30.6	–29.6	18.9	1.3	160	C2′-*endo* (^{2}E)
Lower unit (N_2)	–126.9	–20.3	30.5	–29.1	18.7	1.6	159	C2′-*endo* (^{2}E)

[a] Definitions: χ (O4′–C1′–N1–C2), ν_0 (C4′–O4′–C1′–C2′), ν_1 (O4′–C1′–C2′–C3′), ν_2 (C1′–C2′–C3′–C4′), ν_3 (C2′–C3′–C4′–O4′) and ν_4 (C3′–C4′–O4′–C1′), see Figure 4. [b] For the definition of P and an overview of the terminology used in the description of the sugar puckering modes, see: C. Altona, M. Sundaralingam, *J. Am. Chem. Soc.* **1972**, *94*, 8205–8212.

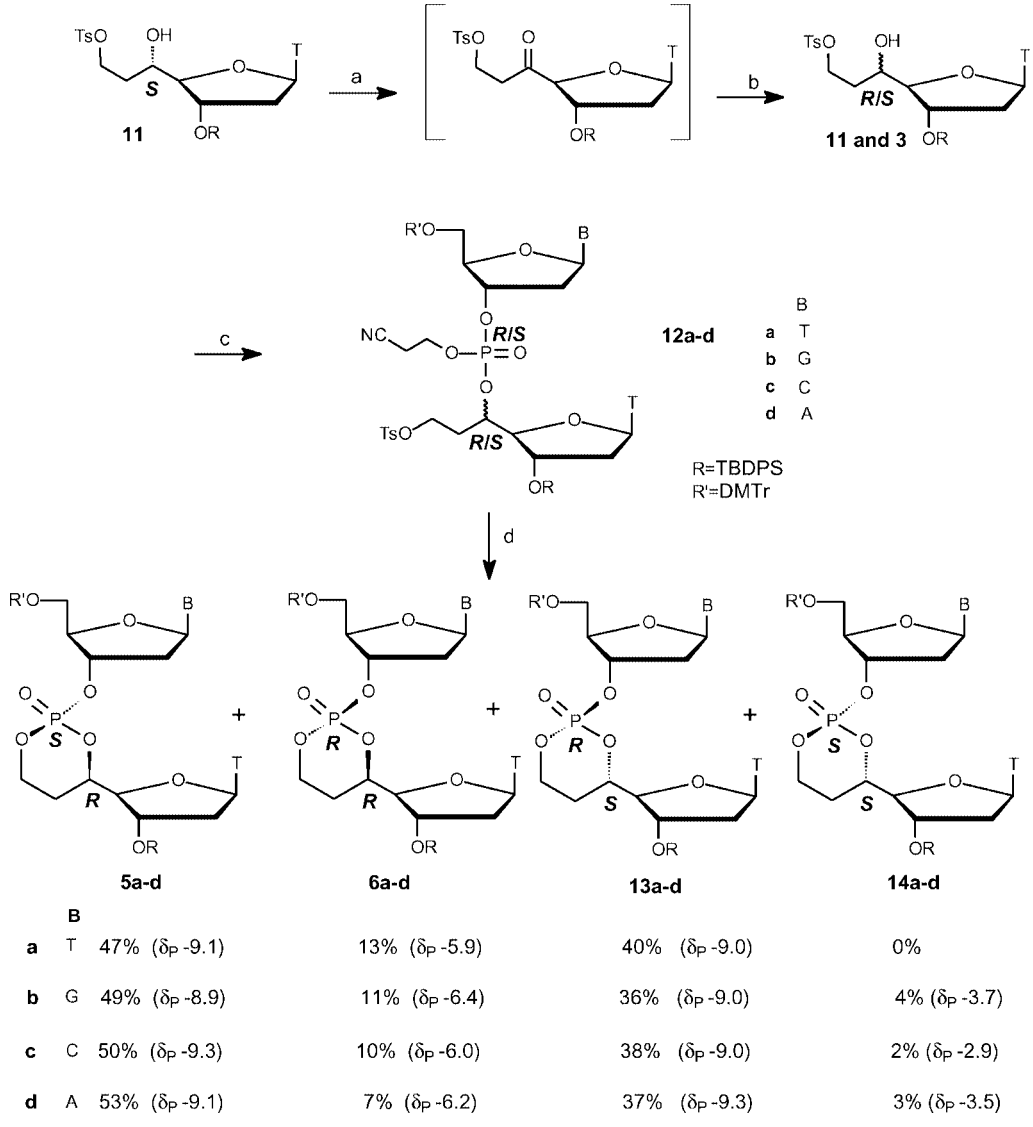
mation previously observed in natural 2′-deoxyribose units.[22] On the basis of the structural data collected for **9**, it can be concluded that the puckering mode of the sugar units of α,β-D-CNA dimers is not dependent on solvation effects.

Table 2. H/H coupling constants [Hz] in the ^{1}H NMR spectra (400 MHz) of α,β-D-CNA TT dimers **9** and **10**.

		J [Hz]				
		J (1′,2′)		*J* (2′,3′)		*J* (3′,4′)
9	upper nucleoside	5.7	8.4	5.8	2.2	2.2
	lower nucleoside	7.0	7.0	6.4	3.5	3.4
10	upper nucleoside	5.7	6.7	5.6	2.0	3.2
	lower nucleoside	6.2	7.9	6.4	3.2	2.8

($S_{C5'}$,S_P)-, ($S_{C5'}$,R_P)-, ($R_{C5'}$,S_P)- and ($R_{C5'}$,R_P)-Configured α,β-D-CNA TT, GT, CT and AT Dimers

Although the synthetic pathway of Scheme 1 gives access to the diastereopure (5′*R*)-*C*-(tosyloxyethyl)thymidine **3** in almost 50% yield from **1**, the overall yield from the starting 5′-*C*-thymidine aldehyde is rather low (25%). In an attempt to increase the overall yield of **3** and to prepare all accessible diastereoisomers of the modified 5′-XT dimers in a one-pot procedure, we opted for a more pragmatic strategy (Scheme 2), which takes advantage of the easier accessibility of the 5′-epimer of **3** (the latter compound, referred to as **11** in Scheme 2, is obtained from the starting aldehyde in ca. 70% overall yield[13]). Oxidation of the 5′-hydroxy function of **11** with the pyridinium dichromate (PDC),[23] immediately followed by the reduction of the corresponding



Scheme 2. Diastereoselective synthesis of the ($R_{C5'}$,S_P)-, ($R_{C5'}$,R_P)-, ($S_{C5'}$,R_P)- and ($S_{C5'}$,S_P)-configured α,β-D-CNA XT dimers (X = T, G, C and A). Reagents and conditions: (a) PDC (pyridinium dichromate), CH_2Cl_2, room temp. (b) $NaBH_4$, EtOH, 0 °C, 90%. (c) 5′-*O*-Dimethoxytrityl-3′-*O*-phosphoramidite-nucleoside (T, G, C and A), tetrazole, CH_3CN, then collidine, I_2/H_2O, 67–92%. (d) K_2CO_3, DMF, room temp., 84–95%.

ketone (with $NaBH_4$) gave a 4:6 diastereoisomeric mixture of **11/3** in a 90% combined yield.

Thus, according to the synthetic route shown in Scheme 2, the tosylated building block **3** was synthesized in four steps and in ca. 40% yield (from the starting aldehyde) compared with five steps and 25% for the approach described in Scheme 1. The diastereoisomeric mixture of **3** and **11** was then treated with the four commercially available nucleoside phosphoramidites under standard conditions[19] to afford the four expected diastereoisomers of the 5′-XT dimers **12a** (X = T), **12b** (X = G), **12c** (X = C) and **12d** (X = A). The dioxaphosphorinane ring structure was directly introduced from the diastereoisomeric mixture **12a–d** in 84–95% yield under milder conditions than those described in Scheme 1 (we used K_2CO_3 at room temperature in preference to Et_3N at 90 °C to avoid any deprotection of the bases). As previously observed,[13] the (5′*S*)-configured acyclic 5′-TT precursor cyclized with complete diastereoselectivity into the ($S_{C5'}$,R_P) diastereoisomer **13a**. Interestingly, cyclization of the corresponding (5′*S*)-configured 5′-XT **12b–d** precursors proceeded in a somewhat less diastereoselective manner (90% *de*, 95% *de* and 92.5% *de*, respectively) giving access to the previously unknown ($S_{C5'}$,S_P) diastereoisomers **14b–d** (in 1%, 0.5% and 0.8% overall yield from **11**, respectively). Cyclization of the (5′*R*)-configured precursors provided the ($R_{C5'}$,S_P) and ($R_{C5'}$,R_P) diastereoisomers (**5a–d** and **6a–d** in Scheme 2) in a more diastereoselective manner (78% *de*, 82% *de*, 83% *de* and 88% *de*, respectively) than previously observed for the (5′*R*)-configured precursor **4** with Et_3N/DMF (70% *de*, Scheme 1). Although the fully protected dimeric building blocks **5a–d**, **6a–d**, **13a–d** and **14c** could be isolated by silica gel chromatography, **14b** and **14d** failed to be separated from **5b** and **13d**, respectively. Nevertheless, after treatment with fluoride (TBAF), the resulting 3′-*O*-deprotected dinucleotides **14′b** and **14′d** could be isolated by reverse-phase HPLC purification. Finally, the dimers **5a** and **6a** (referred to as **5** and **6** in Scheme 1) were obtained from the starting 5′-*C*-thymidine aldehyde in an overall isolated yield of 23% and 6.5%, respectively, compared with 14% and 6% for the first procedure (Scheme 1).

The structure and geometry of the fully protected building blocks **5a–d**, **6a–d**, **13a–d** and **14c** were confirmed by mass spectrometry, and by ^1H, ^{13}C and ^{31}P NMR spectroscopy. The $^3J_{H5'/P}$ values (<1 Hz) assigned to **5a–d** and **13a–d** fit reasonably well with the corresponding values assigned to the unprotected dimer **9**, indicating that the chair conformation of the dioxaphosphorinane linkage is affected neither by the presence of the protective groups nor by the ($R_{C5'}$,S_P) or ($S_{C5'}$,R_P) configuration. Also, we found that the conformational range of the backbone torsion angles α, β and γ assigned for each diastereoisomer of the 5′-TT modified dimers **5a**, **6a** and **13a** remains largely unchanged in the corresponding 5′-GT, 5′-CT and 5′-AT modified dimers.

As observed for the ($R_{C5'}$,R_P)-configured diastereoisomers **6a** and **10**, the value observed for the $^3J_{H5'/P}$ of the ($S_{C5'}$,S_P) diastereoisomer **14c** (4.0 Hz) suggests that the dioxaphosphorinane structure of this isomer is in a twist-chair conformation consistent with the conformational set (α,β) = (t,t). The conformational ranges of α, β and γ (deduced from NMR spectroscopy) are summarized in Table 3 for each α,β-D-CNA diastereoisomer.

Table 3. Summary of the backbone torsion angles α, β and γ of the four possible diastereoisomers of α,β-D-CNA dimeric units.[a]

Diastereoisomer	α	β	γ
($R_{C5'}$,S_P)	g^-	t	g^+
($R_{C5'}$,R_P)	t	t	a^-
($S_{C5'}$,R_P)	g^+	t	g^+
($S_{C5'}$,S_P)	t	t	nd

[a] The torsion angle ranges are indicated as defined in Figure 1 with anticlinal(–) = 240 ± 30° (a^-).

Conclusions

Compared with natural dinucleotides, α,β-D-CNA dimers contain a neutral dioxaphosphorinane linkage, which simultaneously locks the backbone torsion angles α and β of nucleic acids at canonical or noncanonical values. In this paper, the synthesis of the four possible α,β-D-CNA diastereoisomers has been described, and a new strategy has been developed for synthesizing all accessible diastereoisomers of 5′-XT dimers (X = T, G, C and A) in a one-pot procedure. Structural analysis including X-ray crystallography and NMR spectroscopy indicates that the ($R_{C5'}$,S_P) diastereoisomer has its dioxaphosphorinane linkage in a true chair conformation with α and β locked in the typical (g^-,t) conformation found in A- and B-type duplexes. The puckering mode of the 2′-deoxyribose units, however, is clearly C2′-*endo* (S-type), which is characteristic of B-type duplexes. The dioxaphosphorinane linkage of the ($S_{C5'}$,R_P) diastereoisomer also adopts a true chair conformation but with α and β locked in the atypical (g^+,t) conformation frequently observed in bulged or looped regions of nucleic acids and in protein-DNA complexes. The remaining ($R_{C5'}$,R_P) and ($S_{C5'}$,S_P) diastereoisomers are both characterized by the very unusual *trans* conformation of α and β and the twist-chair conformation of their dioxaphosphorinane linkage.

Previous studies[15] have revealed the exceptional duplex-forming ability of oligonucleotides containing canonical D-CNA dimeric units. The formation of stable triplex (and quadruplex) structures could, in principle, benefit from such an approach as well. Several projects are in progress in our laboratory to evaluate the potential advantages of using canonical and noncanonical D-CNA dimers as stabilizing components of biologically important nucleic acid secondary structures.

Experimental Section

3′-*O*-*tert*-Butyldiphenylsilyl-5′-*C*(*R*)-(hydroxyethyl)thymidine (2): To compound **1** (0.5 g, 0.89 mmol), dissolved in acetone (1.5 mL)

and H_2O (0.3 mL), were added *N*-methylmorpholine *N*-oxide (1.03 mL of a 40% solution in H_2O, 10.7 mmol) and osmium tetroxide (40 μL of a 4% solution in H_2O). Stirring was maintained for 16 h, and the reaction was stopped by the addition of aqueous $NaHSO_3$ (1 N, 2 mL) and the mixture diluted with AcOEt. The organic layer was collected, washed with brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the crude material (530 mg) was dissolved in methanol (7 mL) at 0 °C. Sodium periodate (451 mg, 2.1 mmol) was added, and after stirring at 0 °C for 1 h and at room temperature for 2 h, aqueous $NaHSO_3$ (1 N, 3 mL) was added to stop the reaction. After removal of the methanol under reduced pressure, the aqueous layer was extracted with AcOEt (3 × 50 mL), and the organic layer was washed with H_2O and brine and dried with $MgSO_4$. Removal of the solvent provided a white foam (400 mg), which was submitted to sodium borohydride (85 mg, 2.28 mmol) in ethanol (3 mL) at 0 °C. After 12 h of stirring at room temperature, aqueous NH_4Cl was added (5 mL), and the ethanol was removed under reduced pressure. After dilution with AcOEt (50 mL), the organic layer was washed with H_2O and brine and dried with $MgSO_4$. Compound **2** (299 mg, 0.57 mmol, 64% overall yield) was recovered as a white foam after silica gel chromatography with 1:1 AcOEt/dichloromethane as the eluent. TLC: R_f (AcOEt/CH_2Cl_2, 1:1) = 0.35. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.49 (s, 1 H, NH), 7.67–7.39 (m, 11 H, ph and 6-H), 6.20 (dd, J = 9.1, 5.8 Hz, 1 H, 1′-H), 4.53 (m, 1 H, 3′-H), 3.89–3.86 (m, 2 H, 5′-H and 4′-H), 3.67 (m, 1 H, 7′-H), 2.26–2.15 (m, 4 H, 2′-H and 6′-H), 1.67 (s, 3 H, Me), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 164.1, 150.6, 137.8, 135.9, 135.8, 133.2, 130.1, 130.0, 128.0, 127.9, 127.8, 110.9, 91.2, 73.0, 61.2, 40.1, 33.8, 26.9, 19.1, 12.4 ppm. $C_{28}H_{36}N_2O_6Si$ (524.68): calcd. C 64.10, H 6.92, N 5.34; found C 64.05, H 7.01, N 5.31.

3′-*O*-*tert*-Butyldiphenylsilyl-5′-*C*(*R*)-(tosyloxyethyl)thymidine (3): To compound **2** (0.5 g, 0.96 mmol), dissolved in anhydrous pyridine (1 mL) and chloroform (5.2 mL), tosyl chloride (270 mg, 1.4 mmol) was added at 0 °C. Stirring was maintained for 12 h, and the reaction mixture was diluted with AcOEt and washed with saturated aqueous NH_4Cl. The organic layer was collected and washed with H_2O and brine and dried with $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography with 1:1 AcOEt/dichloromethane as the eluent. Compound **3** was recovered as a white foam (501 mg, 0.74 mmol, 77% yield). TLC: R_f (AcOEt/petroleum ether, 1:1) = 0.25. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.11 (s, 1 H, NH), 7.81–7.61 (m, 6 H, ph), 7.39–7.30 (m, 9 H, ph and 6-H), 6.14 (t, J = 6.1 Hz, 1 H, 1′-H), 4.45 (m, 1 H, 3′-H), 4.15–3.75 (m, 4 H, 7′-H, 5′-H and 4′-H), 3.13 (m, 1 H, OH), 2.43 (s, 3 H, MeTs), 2.21 (m, 2 H, 2′-H), 1.89 (s, 3 H, Me), 1.63–1.21 (m, 2 H, 6′-H), 1.08 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 164.0, 150.5, 137.7, 135.9, 135.8, 133.0, 132. 7, 130.2, 129.9, 127.9, 111.1, 90.6, 88.0, 72.6, 67.7, 67.4, 39.6, 31.7, 26.9, 19.1, 12.5 ppm. $C_{35}H_{42}N_2O_8SSi$ (678.87): calcd. C 61.92, H 6.24, N 4.13; found C 62.01, H 6.29, N 4.03.

Cyanoethyl 3′-*O*-(5′-*O*-Dimethoxytrityl)thymidinyl-5′-*C*(*R*)-tosyloxyethyl-3′-(*tert*-butyldiphenylsilyl)thymidinyl Phosphoric Ester (Mixture of Diastereoisomers) (4): Compound **3** (920 mg, 1.35 mmol), thymidine $O_{3'}$-phosphoramidite (3.02 g, 4.05 mmol) and freshly sublimed tetrazole (1.11 g, 16.2 mmol) were dissolved in anhydrous acetonitrile (13 mL) and the mixture was stirred at room temperature for 20 min. After addition of collidine (1.1 mL, 8.11 mmol), the intermediate phosphite was oxidized with iodine (0.1 M solution in 2:1 THF/H_2O) until the dark brown colour persisted. The reaction mixture was diluted with AcOEt and washed with aqueous sodium thiosulfate (15%) to remove excess iodine. The organic layer was washed with H_2O and brine, and the solvent was removed in vacuo. The crude material was chromatographed on silica gel with 9:1 AcOEt/petroleum ether as the eluent. After evaporation of the solvent, compound **4** (mixture of diastereoisomers) was recovered as a white foam (1.68 g, 93% yield). TLC: R_f (AcOEt) = 0.52. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.93 (s, 4 H, NH), 9.89 (s, 4 H, NH), 9.87 (s, 4 H, NH), 9.70 (s, 4 H, NH), 7.50–6.80 (m, 29 H, ph and 6-H), 6.42 (2m, 2 H, 1′-H), 6.15 (2m, 2 H, 1′-H), 5.05 (m, 1 H, 3′-H), 4.10 (m, 8 H, 3′-H, 4′-H, 5′-H and 2 CH_2), 3.76 (s, 6 H, Me DMTr), 2.67 (m, 2 H), 2.44 (s, 3 H, Me Ts), 2.24 (m, 4 H), 1.84 (s, 6 H, 2 Me), 1.25–1.21 (2m, 4 H), 1.41–1.38 (2m, 4 H), 1.04 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 164.5, 164.1, 158.8, 150.9, 150.6, 141.1, 135.8, 135.1, 132.8, 132.6, 130.2, 130.0, 128.0, 127.3, 121.6, 113.4, 111.4, 87.2, 86.4, 85.5, 84.4, 80.0, 73.9, 65.8, 62.6, 61.9, 55.4, 55.3, 39.6, 38.3, 27.8, 26.9, 21.7, 19.5, 19.4, 19.1, 11.7 ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = –3.5 and –3.4 ppm. MS (FAB): m/z = 1360 [M + Na]$^+$, 1338 [M + H]$^+$, 1036 [M – DMTr+2H]$^+$.

5′-*O*-Dimethoxytrityl-3′-*O*-*tert*-butyldiphenylsilyl-α,β-D-CNA TT (R_C,S_P) (5) and 5′-*O*-Dimethoxytrityl-3′-*O*-*tert*-butyldiphenylsilyl-α,β-D-CNA TT (R_C,R_P) (6): To a solution of **4** (770 mg, 0.57 mmol) in anhydrous DMF (20 mL), was added Et_3N (319 μL, 2.28 mmol). After 3 h of stirring at 90 °C, the reaction mixture was cooled and diluted with AcOEt (100 mL) and washed with H_2O (3 × 20 mL) and brine. The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo. The cyclic phosphotriesters **5** and **6** were recovered as white foams. Compounds **5** (400 mg, 0.36 mmol) and **6** (171 mg, 0.15 mmol) were isolated (90% yield) after silica gel chromatography with AcOEt as the eluent.

Data for 5: TLC: R_f (AcOEt) = 0.50. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.59 (2 s, 2 H, NH), 9.44 (2 s, 2 H, NH), 7.72–6.84 (m, 25 H, ph, 6a-H and 6b-H), 6.38 (m, 2 H, 1′b-H and 1′a-H), 5.21 (m, $J_{H/P}$ = 5.7 Hz, 1 H, 3′a-H), 4.58 (m, 1 H, 3′b-H), 4.49 (ddd, J = 11.7, 4.4 and 2.5 Hz, $J_{H/P}$ < 1 Hz, 1 H, 5′b-H), 4.20 (m, 1 H, 4′a-H), 4.17 (m, 1 H, 7′b-H), 4.10 (m, 1 H, 7′b-H), 4.01 (m, 1 H, 4′b-H), 3.81 (s, 6 H, Me DMTr), 3.50 (A part of an ABX system, J = 10.7 and 3.0 Hz, 1 H, 5′a-H), 3.39 (B part of an ABX system, J = 10.6 and 2.4 Hz, 1 H, 5′a-H), 2.40 (m, 1 H, 2′a-H), 2.29 (m, 1 H, 2′a-H), 2.23 (m, 2 H, 2′b-H), 1.86 (s, 3 H, Me), 1.51 (2m, 2 H, 6′b-H), 1.42 (2m, 2 H, 6′b-H), 1.38 (s, 3 H, Me), 1.09 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 164.2, 159.2, 151.0, 144.4, 143.7, 139.9, 136.6, 136.4, 136.0, 135.4, 135.3, 133.3, 133.1, 131.4, 130.6, 130.5, 128.5, 128.4, 127.7, 113.7, 112.4, 111.6, 88.5, 87.7, 86.4, 84.9, 84.4, 80.4, 79.2, 73.2, 68.5, 63.7, 55.7, 39.8, 39.0, 30.1, 29.8, 27.6, 27.3, 19.5, 13.0, 12.0 ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = –9.1 ppm. $C_{59}H_{65}N_4O_{14}PSi$ (1113.24): calcd. C 63.66, H 5.89, N 5.03; found C 63.27, H 5.81, N 5.13.

Data for 6: TLC: R_f (AcOEt) = 0.20. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.38 (2 s, 2 H, NH), 9.27 (2 s, 2 H, NH), 7.69–6.84 (m, 25 H, ph, 6a-H and 6b-H), 6.44 (dd, J = 9.4 and 5.4 Hz, 1 H, 1′a-H), 6.35 (dd, J = 8.5 and 5.7 Hz, 1 H, 1′b-H), 5.20 (m, $J_{H/P}$ = 6.0 Hz, 1 H, 3′a-H), 4.52 (m, 2 H, 3′b-H and 5′b-H), 4.32 (m, 1 H, 7′b-H), 4.17 (m, 1 H, 7′b-H), 4.09 (br. s, 1 H, 4′a-H), 3.98 (m, 1 H, 4′b-H), 3.80 (s, 6 H, Me DMTr), 3.44 (A part of an ABX system, J = 10.6 and 2.1 Hz, 1 H, 5′a-H), 3.30 (B part of an ABX system, J = 11.0 and 2.6 Hz, 1 H, 5′a-H), 2.56 (m, J = 13.8 and 5.4 Hz, 1 H, 2′a -H), 2.39 (m, J = 14.1, 9.3 and 5.1 Hz, 1 H, 2′a-H), 2.27 (m, J = 13.3, 5.9 and < 1 Hz, 1 H, 2′b-H), 2,03 (m, J = 13.5, 8.4 and 5.5 Hz, 1 H, 2′b-H), 1.82 (d, J = 1.1 Hz, 3 H, b-Me), 1.41 (m, 2 H, 6′b-H), 1.37 (d, J = 1.1 Hz, 3 H, a-Me), 1.09 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 164.2, 164.1, 159.2, 151.0, 150.7, 144.4, 136.2, 136.1, 135.4, 135.3, 133.2, 133.1, 130.7, 130.5, 128.5, 128.4, 127.8, 113.8, 112.3, 111.9, 88.5, 87.8, 86.7, 85.1, 84.6,

80.7, 79.8, 73.3, 68.4, 63.9, 55.7, 40.0, 39.0, 27.2, 19.5, 13.0, 12.0 ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = –5.9 ppm. $C_{59}H_{65}N_4O_{14}PSi$ (1113.24): calcd. C 63.66, H 5.89, N 5.03; found C 63.11, H 5.71, N 5.22.

5′-*O*-Dimethoxytrityl-α,β-D-CNA TT (R_C,S_P) (7) and 5′-*O*-Dimethoxytrityl-α,β-D-CNA TT (R_C,R_P) (8): To compound **5** (0.7 g, 0.63 mmol) or **6** (0.15 g, 0.13 mmol), dissolved in anhydrous THF (5 mL, 1.5 mL for **6**), tetrabutylammonium fluoride (0.7 mL, 0.7 mmol or 0.15 mL for **6**) was added at room temperature. Stirring was maintained for 1 h. After removal of the solvent under reduce pressure, the crude product was purified on a silica gel column with 95:5 AcOEt/methanol as the eluent. Compound **7** (or **8**) was recovered as a white foam (473 mg, 90% yield or 97 mg, 86% yield for **8**). Probably due to the formation of aggregates in solution, the NMR spectra were obtained with a very poor resolution for ^{1}H and without detection of the aliphatic carbon atoms in the ^{13}C spectrum. This phenomenon has already been observed with the (S_C,R_P)-configured α,β-D-CNA diastereoisomer (see supporting information of ref.[13]).

Data for 7: TLC: R_f (5% MeOH/AcOEt) = 0.15. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.15 (s, 2 H, NH), 9.92 (s, 2 H, NH), 7.52–7.19 (m, 11 H, ph and 6-H), 6.80 (m, 4 H, ph), 6.43 (m, 1 H, 1′-H), 6.22 (m, 1 H, 1′-H), 5.22 (m, 1 H, 3′-H), 4.66 (m, 3 H), 4.31 (m, 4 H), 4.22 (m, 4 H), 3.96 (m, 2 H), 3.76 (s, 6 H, MeO), 3.35 (m, 2 H), 2.64 (m, 2 H), 2.35 (m, 2 H), 2.13 (m, 3 H), 1.84 (s, 3 H, Me), 1.38 (s, 3 H, Me) ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = –8.7 ppm. MS (electrospray): *m*/*z* = 897.3 [M + Na]$^+$, 919 [M + K]$^+$.

Data for 8: TLC: R_f (5% MeOH/AcOEt) = 0.12. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.10 (s, 2 H, NH), 9.90 (s, 2 H, NH), 7.56–7.20 (m, 11 H, ph and 6-H), 6.82 (m, 4 H, ph), 6.43 (dd, *J* = 9.1 and 5.2 Hz, 1 H, 1′-H), 6.26 (t, *J* = 6.7 Hz, 1 H, 1′-H), 5.11 (m, 1 H, 3′-H), 4.62 (m, 4 H), 4.47 (m, 4 H), 4.02 (m, 2 H), 3.77 (s, 6 H, MeO), 3.42 (m, 2 H), 2.62 (m, 2 H), 2.30 (m, 2 H), 2.11 (m, 3 H), 1.84 (s, 3 H, Me), 1.38 (s, 3 H, Me) ppm.^{31}P NMR (81 MHz, $CDCl_3$): δ = –7.7 ppm. MS (ESI): *m*/*z* = 897.3 [M + Na]$^+$, 919 [M + K]$^+$.

α,β-D-CNA TT (R_C,S_P) (9) and α,β-D-CNA TT (R_C,R_P) (10): Compound **7** (300 mg, 0.34 mmol) or **8** (70 mg, 0.08 mmol) was dissolved in TFA/dichloromethane (2%, 7 mL or 2 mL for **8**) at room temperature. After 15 min, the red solution was concentrated to dryness. The crude material was dissolved in THF and purified by silica gel chromatography. It was first eluted with AcOEt to remove the dimethoxytrityl residue and then with 4:1 AcOEt/methanol to collect the (R_C,S_P)-configured diastereoisomer **9** [or the (R_C,R_P)-configured diastereoisomer **10**] obtained as a white foam after evaporation of the solvent (**9**: 166 mg, 85% yield, **10**: 35 mg, 77% yield).

Data for 9: TLC: R_f (15% MeOH/AcOEt) = 0.25. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.82 (d, *J* = 1.2 Hz, 1 H, 6a-H), 7.54 (d, *J* = 1.2 Hz, 1 H, 6b-H), 6.35 (dd, *J* = 5.7 and 8.4 Hz, 1 H, 1′a-H), 6.31 (t, *J* = 7.0 Hz, 1 H, 1′b-H), 5.11 (dddd, *J* = 2.2, 2.2, 5.8 Hz and $J_{H/P}$ = 5.9 Hz, 1 H, 3′a-H), 4.86 (ddd, *J* = 2.1, 4.2 and 11.5 Hz, 1 H, 5′b-H), 4.61 (ddd, *J* = 3.4, 3.5 and 6.6 Hz, 1 H, 3′b-H), 4.56–4.54 (m, $J_{H/P}$ = 3.0 and 20 Hz, 2 H, 7′b-H), 4.27 (dd, *J* = 2.2 and 3.2 Hz, 1 H, 4′a-H), 3.93 (ddd, *J* = 3.3, 4.3 Hz and $J_{H/P}$ = 3.2 Hz, 1 H, 4′b-H), 3.84 (A part of an ABX system, *J* = 12.0, and 3.2 Hz, 1 H, 5′a-H), 3.82 (B part of an ABX system, *J* = 12.0, and 3.2 Hz, 1 H, 5′a-H), 2.59 (A part of an ABX system, *J* = 14.2, 5.8 and 2.1 Hz, 1 H, 2′a-H), 2.41 (B part of an ABX system, *J* = 14.2, 8.4 and 5.8 Hz, 1 H, 2′a-H), 2.37 (m, 1 H, 2′b-H), 2.27 [B part of an ABX(Y) system, *J* = 13.8, 6.4, and 3.5 Hz, 1 H, 2′b-H], 2.20 (m, 1 H, 6′b-H), 2.04 [A part of an ABX(Y) system, *J* = 12.4, 2.0, and 2.0 Hz, 1 H, 6′b-H], 1.91 (d, 3 H, b-Me), 1.90 (d, 3 H, a-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 165.1, 165.0, 151.1, 136.6, 110.8, 87.3, 85.9, 85.1, 84.9, 80.7, 78.8, 69.9, 69.0, 61.4, 39.1, 38.2, 27.6, 11.4, 11.3 ppm. ^{31}P NMR (121 MHz, CD_3OD): δ = –6.4 ppm. $C_{22}H_{29}N_4O_{12}P$ (572.46): calcd. C 46.26, H 5.11, N 9.79; found C 45.95, H 5.18, N 9.88.

Data for 10: TLC: R_f (20% MeOH/AcOEt) = 0.48. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.79 (d, *J* = 1.2 Hz, 1 H, 6a-H), 7.52 (d, *J* = 1.1 Hz, 1 H, 6b-H), 6.31 (dd, *J* = 6.7 and 5.7 Hz, 1 H, 1′a-H), 6.29 (dd, *J* = 7.9 and 6.2 Hz, 1 H, 1′b-H), 5.13 (dddd, *J* = 2.0, 3.2, 5.6 Hz and $J_{H/P}$ = 6.4 Hz, 1 H, 3′a-H), 4.91 (ddd, *J* = 2.8, 5.2, 10.8 Hz and $J_{H/P}$ = 4.0 Hz, 1 H, 5′b-H), 4.61 (m, $J_{H7'b/P}$ = 10.4 Hz, $J_{H7'a/P}$ = 12.4 Hz, 2 H, 7′-H), 4.57 (m, 1 H, 3′b-H), 4.23 (t, *J* = 3.2, 3.2 Hz, 1 H, 4′a-H), 3.99 (ddd, *J* = 2.8, 5.2 Hz and $J_{H4'b/P}$ = 2.4 Hz, 1 H, 4′b-H), 3.81 and 3.79 (AB part of an ABX system, *J* = 3.2, 3.2 and 12.0 Hz, 2 H, 5′a-H), 2.53 (A part of an ABX system, *J* = 14.0, 5.6 and 1.6 Hz, 1 H, 2′a-H), 2.41 (B part of an ABX system, *J* = 14.0, 6.7, 5.6 Hz and $J_{H2'a/P}$ = 1.2 Hz, 1 H, 2′a-H), 2.29 (m, 2 H, 2′b-H),2.25 (m, 1 H, 6′b-H), 2.15 (m, *J* = 12.0, 2.8 and 2.8 Hz, 1 H, 6′b-H), 1.91 (d, *J* = 1.1 Hz, 3 H, b-Me). 1.90 (d, 3 H, *J* = 1.2 Hz, a-Me) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 165.1, 165.0, 151.1, 136.7, 136.6, 110.8, 110.7, 87.3, 86.0, 85.9, 85.0, 81.7, 79.8, 70.5, 68.0, 61.4, 39.0, 38.3, 28.7, 11.3, 11.2 ppm. ^{31}P NMR (121 MHz, CD_3OD): δ = –3.8 ppm. $C_{22}H_{29}N_4O_{12}P$ (572.46): calcd. C 46.26, H 5.11, N 9.79; found C 46.81, H 5.07, N 9.80.

Cyanoethyl 3′-*O*-(5′-*O*-Dimethoxytrityl)thymidinyl-5′-*C*-tosyloxyethyl-3′-(*tert*-butyldiphenylsilyl)thymidinyl Phosphoric Ester (12a), Cyanoethyl 3′-*O*-(5′-*O*-Dimethoxytrityl)-*N*-isobutylguanidinyl-5′-*C*-tosyloxyethyl-3′-(*tert*-butyldiphenylsilyl)thymidinyl Phosphoric Ester (12b), Cyanoethyl 3′-*O*-(5′-*O*-Dimethoxytrityl)-*N*-benzoylcytidinyl-5′-*C*-tosyloxyethyl-3′-(*tert*-butyldiphenylsilyl)thymidinyl Phosphoric Ester (12c) and Cyanoethyl 3′-*O*-(5′-*O*-Dimethoxytrityl)-*N*-benzoyladenidinyl-5′-*C*-tosyloxyethyl-3′-(*tert*-butyldiphenylsilyl)thymidinyl Phosphoric Ester (12d): Dinucleotides **12a**–**d** were prepared according to the protocol described for **4**, starting in each case from 0.5 g of a (5′*R*/*S*) mixture of 3′-*O*-*tert*-butyldiphenylsilyl-5′-*C*-(tosyloxyethyl)thymidine and with commercially available phosphoramidite. After silica gel chromatography, compounds **12a**–**d** were isolated as white foams in 88%, 78%, 67% and 92% yield, respectively. Since a mixture of four diastereoisomers is obtained in each case, the corresponding ^{1}H and ^{13}C NMR spectra are very complicated and are, therefore, not described.

Data for 12a: TLC: R_f (AcOEt) = 0.55. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –2.6, –2.7, –3.4, –3.5 ppm. MS (ESI): *m*/*z* = 1360 [M + Na]$^+$, 1338 [M + H]$^+$, 1036 [M – DMTr + 2 H]$^+$.

Data for 12b: TLC: R_f (AcOEt) = 0.35. ^{31}P NMR (81 MHz, $CDCl_3$): δ = –2.8, –3.0, –3.1, –3.8 ppm. MS (ESI): *m*/*z* = 1434 [M + H]$^+$, 1131 [M – DMTr + 2 H]$^+$.

Data for 12c: TLC: R_f (AcOEt) = 0.45. ^{31}P NMR (81 MHz, $CDCl_3$): δ = –2.8, –3.5, –3.6, –3.7 ppm. MS (ESI): *m*/*z* = 1465 [M + K]$^+$, 1449 [M + Na]$^+$, 1423 [M + H]$^+$.

Data for 12d: TLC: R_f (AcOEt) = 0.40. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –2.8, –2.9, –3.4, –3.6 ppm. MS (ESI): *m*/*z* = 1473.7 [M + Na]$^+$, 1451.6 [M + H]$^+$, 1149.4 [M – DMTr + 2 H]$^+$.

5′-*O*-Dimethoxytrityl-3′-*O*-*tert*-butyldimethylsilyl-α,β-D-CNA G^{iBu}T (R_C,S_P) (5b), (R_C,R_P) (6b), (S_C,R_P) (13b) and (S_C,S_P) (14b), 5′-*O*-Dimethoxytrityl-3′-O-*tert*-butyldiphenylsilyl-α,β-D-CNA C^{Bz}T (R_C,S_P) (5c), (R_C,R_P) (6c), (S_C,R_P) (13c) and (S_C,S_P) (14c) and 5′-*O*-Dimethoxytrityl-3′-*O*-*tert*-butyldiphenylsilyl-α,β-D-CNA A^{Bz}T (R_C,S_P) (5d), (R_C,R_P) (6d), (S_C,R_P) (13d) and (S_C,S_P) (14d): The α,β-D-CNA dimers **5a**–**d**, **6a**–**d**, **13a**–**d** and **14a**–**d** were obtained in

90%, 91%, 95% and 84% yield, respectively, from the corresponding dinucleotides according to the following protocol: to dinucleotide **12a–d** (0.5 mmol) in anhydrous DMF (20 mL), was added potassium carbonate (1.1 g, 8 mmol). After 4 h of stirring at 25 °C, the excess of base was filtered off, and the reaction mixture was diluted with AcOEt (100 mL) and washed with H_2O (3 × 20 mL) and brine. The organic layer was dried with $MgSO_4$, and the solvent was removed in vacuo. **5a** (identical to **5**), **6a** (identical to **6**) and **13a** were separated by silica gel chromatography with AcOEt as the eluent. TLC: R_f (AcOEt) = 0.50 (**5a**), 0.35 (**13a**) and 0.2 (**6a**). Data for **13a** are provided in ref.[13] **5b**/**14b**, **6b** and **13b** were separated by reverse-phase chromatography on a Kromasil C_{18}, 7 μm, 100 Å, 250 × 4.6 mm column for analysis or a 250 × 20 mm preparatory scale column with 30:70 H_2O/acetonitrile. t_r = 29.48 min, 20.18 min and 21.8 min, respectively.

Data for 5b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.00 (s, 1 H, NH), 8.82 (s, 1 H, NH), 7.69–7.22 (m, 21 H, ph, 6_T-H and 2_G-H), 6.82 (B part of AB syst, J = 8.7 Hz, 4 H, DMT), 6.81 (B part of AB syst, J = 8.7 Hz, 4 H, DMT), 6.50 (t, J = 7.4 Hz, 1 H, $1'_T$-H), 6.13 (dd, J = 5.4 and 9.0 Hz, 1 H, $1'_G$-H), 5.38 (t, J = 5.3 Hz, 1 H, $3'_G$-H), 4.61 (m, 1 H, $3'_T$-H), 4.37 (br. d, J = 12.3 Hz, $J_{H/P} < 1$ Hz, 1 H, $5'_T$-H), 4.15–3.89 (m, 4 H, $7'_T$-H, $4'_G$-H and $4'_T$-H), 3.78 (s, 6 H, MeO), 3.36 (AB part of an ABX syst, J = 3.9, 5.7 and 10.2 Hz, 2 H, $5'_G$-H), 3.23 (AB part of an ABX syst, J = 3.9, 5.7 and 10.2 Hz, 2 H, $5'_G$-H), 2.82 (sept, J = 6.9 Hz, 1 H, CH *i*Bu), 2.73 (A part of an ABX syst, J = 0.9, 5.7 and 13.8 Hz, 1 H, $2'_G$-H), 2.45 (B part of an ABX syst, J = 5.4, 9.0 and 13.8 Hz, 1 H, $2'_G$-H), 2.34 (m, 2 H, $2'_T$-H), 2.01 (s, 3 H, Me), 1.27–1.15 (m, 1 H, $6'_T$-H), 1.21 (d, J = 6.9 Hz, 3 H, Me *i*Bu), 1.17 (d, J = 6.6 Hz, 3 H, Me *i*Bu), 1.08 (s, 9 H, *t*Bu), 1.05–1.02 (m, 1 H, $6'_T$-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.1, 164.7, 158.7, 155.6, 150.6, 148.5, 148.0, 144.3, 136.6, 136.2, 135.9, 135.7, 135.2, 132.8, 132.5, 130.6, 130.0, 128.2, 128.0, 127.1, 121.3, 113.3, 111.2, 88.6, 88.5, 86.9, 85.6, 84.6, 84.5, 83.7, 81.3, 78.3, 72.3, 68.3, 63.1, 60.4, 55.3, 39.2, 38.8, 35.7, 29.3, 26.9, 26.6, 19.2, 19.1, 18.8, 12.7 ppm.^{31}P NMR (121 MHz, $CDCl_3$): δ = –8.9 ppm. MS (ESI): m/z = 1230.7 $[M + Na]^+$, 1208.8 $[M + H]^+$.

Data for 6b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.00 (s, 1 H, NH), 8.71 (s, 1 H, NH), 7.72 (s, 1 H, 2_G-H), 7.64–7.17 (m, 20 H, ph and 6_T-H), 6.78 (B part of AB syst, J = 9.0 Hz, 4 H, DMT), 6.77 (B part of AB syst, J = 9.0 Hz, 4 H, DMT), 6.11 (t, J = 6.6 Hz, 1 H, $1'_T$-H), 6.08 (dd, J = 5.4 and 8.4 Hz, 1 H, $1'_G$-H), 5.25 (m, 1 H, $3'_G$-H), 4.60 (m, 1 H, $5'_T$-H), 4.51 (m, 1 H, $3'_T$-H), 4.34 (m, 1 H, $7'_T$-H), 4,21 (m, 1 H, $4'_G$-H), 4.20–4.07 (m, 1 H, $7'_T$-H), 4.02 (m, 1 H, $4'_T$-H), 3.77 (2s, 6 H, MeO), 3.33 (AB part of an ABX syst, J = 3.6, 3.6 and 10.5 Hz, 2 H, $5'_G$-H), 3.19 (AB part of an ABX syst, J = 3.6, 3.6 and 10.5 Hz, 2 H, $5'_G$-H), 2.86 (m, 1 H, $2'_G$-H), 2.50 (m, 1 H, $2'_G$-H), 2.34 (m, 1 H, $2'_T$-H), 2.22 (sept, J = 6.6 Hz, 1 H, CH *i*Bu), 2.07 (m, 1 H, $2'_T$-H), 1.86 (br. s, 3 H, Me), 1.61–1.47 (m, 1 H, $6'_T$-H), 1.39–1.32 (m, 1 H, $6'_T$-H), 1.09 (d, J = 6.6 Hz, Me 3 H, *i*Bu), 1.05 (s, 9 H, *t*Bu), 0.96 (d, J = 6.6 Hz, 3 H, Me *i*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.3, 164.2, 158.7, 155.5, 150.2, 148.0, 147.9, 144.4, 136.6, 135.8, 135.7, 135.5, 135.3, 132.8, 132.7, 130.3, 130.1, 128.2, 128.0, 127.2, 121.9, 113.3, 113.0, 111.0, 88.3, 88.2, 87.4, 86.6, 84.5, 84.4, 84.1, 79.6, 78.9, 72.6, 67.2, 63.0, 60.4, 55.2, 40.3, 38.6, 36.0, 26.8, 26.6, 19.1, 18.9, 18.8, 12.4 ppm.^{31}P NMR (121 MHz, $CDCl_3$): δ = –6.4 ppm. MS (ESI): m/z = 1230.7 $[M + Na]^+$, 1208.8 $[M + H]^+$.

Data for 13b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.14 (s, 1 H, NH), 8.69 (s, 1 H, NH), 7.66 (s, 1 H, 2_G-H), 7.65–7.18 (m, 20 H, ph and 6_T-H), 6.75 (B part of AB syst, J = 9.0 Hz, 4 H, DMT), 6.72 (B part of AB syst, J = 9.0 Hz, 4 H, DMT), 6.36 (dd, J = 6.0 and 8.7 Hz, 1 H, $1'_T$-H), 6.17 (dd, J = 5.4 and 8.4 Hz, 1 H, $1'_G$-H), 5.38 (m, 1 H, $3'_G$-H), 4.33–4.24 (m, 1 H, $7'_T$-H), 4.29 (m, 1 H, $3'_T$-H), 4,21 (m, 1 H, $4'_G$-H), 4.13–4.05 (m, 1 H, $7'_T$-H), 3.87 (m, $J_{H/P} < 1$ Hz, 1 H, $5'_T$-H), 3.82 (m, 1 H, $4'_T$-H), 3.74 (2s, 6 H, MeO), 3.34 (AB part of an ABX syst, J = 2.7, 3.3 and 10.8 Hz, 2 H, $5'_G$-H), 3.17 (AB part of an ABX syst, J = 2.7, 3.3 and 10.8 Hz, 2 H, $5'_G$-H), 3.10 (m, 1 H, $2'_G$-H), 2.56 (B part of an ABX syst, J = 2.4, 5.7 and 13.2 Hz, 1 H, $2'_G$-H), 2.36–2.16 (m, 3 H, $2'_T$-H and CH *i*Bu), 1.94 (br. s, 3 H, Me), 1.94–1.82 (m, 1 H, $6'_T$-H), 1.25–1.22 (m, 1 H, $6'_T$-H), 1.08 (d, J = 6.6 Hz, 3 H, Me *i*Bu), 1.07 (s, 9 H, *t*Bu), 0.94 (d, J = 6.6 Hz, 3 H, Me *i*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.6, 164.5, 158.6, 155.6, 150.7, 148.1, 147.9, 144.4, 136.4, 135.8, 135.7, 135.5, 135.4, 133.2, 132.5, 130.3, 130.0, 128.1, 127.9, 127.0, 121.7, 113.2, 111.6, 88.2, 88.1, 86.6, 86.3, 84.7, 84.1, 79.9, 77.8, 74.4, 67.8, 62.9, 60.4, 55.2, 39.8, 38.1, 35.9, 27.5, 26.9, 19.0, 18.9, 18.7, 12.3 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –9.0 ppm. MS (ESI): m/z = 1230.7 $[M + Na]^+$, 1208.8 $[M + H]^+$.

5c, **6c**, and **13c**/**14c** were separated by silica gel chromatography with AcOEt as the eluent. TLC: R_f (AcOEt) = 0.30 (**5c**), 0.20 (**13c**/**14c**) and 0.15 (**6c**). **13c** was separated from **14c** on a Kromasil C_{18}, 7 μm, 100 Å, 250 × 20 mm column with 90:10 MeOH/H_2O as the eluent. t_r = 18.9 min for **14c** and 22.4 min for **13c**.

Data for 5c: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.77 (s, 1 H, NH), 8.36 (s, 1 H, NH), 8.05 (d, J = 7.5 Hz, 1 H, 6_C-H), 7.88 (d, J = 7.5 Hz, 2 H, ph), 7.67–7.22 (m, 24 H, ph, 5_C-H, and 6_T-H), 6.85 (m, 4 H, DMT), 6.37 (t, J = 7.3 Hz, 1 H, $1'_T$-H), 6.25 (t, J = 6.4 Hz, 1 H, $1'_C$-H), 5.11 (m, 1 H, $3'_C$-H), 4.54 (m, 1 H, $3'_T$-H), 4.37 (m, $J_{H/P} < 1$ Hz, 1 H, $5'_T$-H), 4.29 (m, 1 H, $4'_C$-H), 4.14–4.05 (m, 2 H, $7'_T$-H), 3.95 (m, 1 H, $4'_T$-H), 3.78 (s, 6 H, MeO), 3.46 (AB part of an ABX syst, J = 3.3, 3.6 and 10.9 Hz, 2 H, $5'_C$-H), 3.40 (AB part of an ABX syst, J = 3.3, 3.6 and 10.9 Hz, 2 H, $5'_C$-H), 2.65 (m, 1 H, $2'_C$-H), 2.21–2.12 (m, 3 H, $2'_T$-H and $2'_C$-H), 1.83 (br. s, 3 H, Me), 1.60–1.32 (m, 2 H, $6'_T$-H), 1.06 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 162.8, 158.8, 150.8, 144.1, 143.9, 136.0, 135.8, 135.1, 134.9, 133.1, 132.9, 132.8, 130.2, 130.1, 128.9, 128.1, 128.0, 127.9, 127.3, 113.4, 111.4, 97.0, 88.1, 88.0, 87.3, 86.7, 85.4, 85.0, 84.9, 80.1, 77.6, 72.9, 68.1, 62.6, 55.3, 40.0, 39.4, 27.2, 26.9, 19.1, 12.6 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –9.3 ppm. MS (ESI): m/z = 1203.1 $[M + H]^+$.

Data for 6c: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (s, 1 H, NH), 8.16 (s, 1 H, NH), 8.07 (d, J = 7.5 Hz, 1 H, 6_C-H), 7.90 (d, J = 7.5 Hz, 2 H, ph), 7.68–7.21 (m, 23 H, ph, 5_C-H), 7.17 (br. d, 1 H, 6_T-H), 6.84 (B part of AB syst, J = 9.0 Hz, 4 H, DMT), 6.35 (dd, J = 5.7 and 8.7 Hz, 1 H, $1'_T$-H), 6.23 (dd, J = 5.4 and 7.5 Hz, 1 H, $1'_C$-H), 5.12 (m, 1 H, $3'_C$-H), 4.55–4.49 (m, 2 H, $3'_T$-H and $5'_T$-H), 4.34–4.26 (m, 1 H, $7'_T$-H), 4.22 (m, 1 H, $4'_C$-H), 4.19–4.11 (m, 1 H, $7'_T$-H), 3.97 (m, 1 H, $4'_T$-H), 3.79 (s, 6 H, MeO), 3.37 (d, 1 H, $5'_C$-H), 2.86 (m, 1 H, $2'_C$-H), 2.31–2.20 (m, 2 H, $2'_T$-H and $2'_C$-H), 2.06–1.97 (m, 1 H, $2'_T$-H), 1.83 (br. s, 3 H, Me), 1.47–1.27 (m, 2 H, $6'_T$-H), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 163.2, 158.8, 150.9, 144.1, 143.8, 135.6, 135.1, 135.0, 134.9, 133.2, 133.1, 133.0, 132.5, 130.4, 130.3, 130.0, 128.8, 128.1, 128.0, 127.9, 127.2, 113.4, 112.2, 97.3, 87.7, 87.6, 87.4, 87.2, 85.8, 85.7, 84.6, 79.8, 78.9, 74.4, 67.7, 63.1, 55.2, 40.5, 39.9, 27.5, 26.8, 19.0, 12.3 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –6.0 ppm. MS (ESI): m/z = 1203.1 $[M + H]^+$.

Data for 13c: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.70 (s, 1 H, NH), 8.16 (s, 1 H, NH), 7.99 (d, J = 7.2 Hz, 1 H, 6_C-H), 7.84 (d, J = 7.5 Hz, 2 H, ph), 7.58–7.22 (m, 20 H, ph, 5_C-H, and 6_T-H), 7.16 (A part of an AB syst, J = 1.5 and 8.7 Hz, 4 H, DMT), 6.77 (B part of AB syst, J = 8.7 Hz, 4 H, DMT), 6.61 (dd, J = 5.4 and

9.3 Hz, 1 H, 1′$_T$-H), 6.31 (dd, J = 5.4 and 8.1 Hz, 1 H, 1′$_C$-H), 5.09 (t, J = 5.4 Hz, 1 H, 3′$_C$-H), 4.42–4.30 (m, 1 H, 7′$_T$-H), 4.37 (d, J = 5.7 Hz, 1 H, 3′$_T$-H), 4.30 (s, 1 H, 4′$_C$-H), 4.15–4.07 (m, 1 H, 7′$_T$-H), 3.71 (s, 6 H, MeO), 3.70 (m, 1 H, 4′$_T$-H), 3.48 (br. d, J = 11.1 Hz, $J_{H/P}$ < 1 Hz, 1 H, 5′$_T$-H), 3.41 (m, 2 H, 5′$_C$-H), 2.86 (m, 1 H, 2′$_C$-H), 2.34–2.17 (m, 3 H, 6′$_T$-H, 2′$_T$-H and 2′$_C$-H), 1.92–1.82 (m, 1 H, 2′$_T$-H), 1.94 (br. s, 3 H, Me), 1.32–1.27 (m, 1 H, 6′$_T$-H), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7, 162.5, 158.8, 150.3, 144.3, 143.9, 135.9, 135.8, 134.9, 133.2, 133.1, 132.8, 132.7, 130.4, 130.3, 130.2, 130.1, 130.0, 129.0, 128.1, 127.7, 127.3, 113.4, 111.5, 97.3, 88.2, 88.1, 87.3, 87.1, 86.2, 85.6, 85.5, 79.5, 79.4, 79.3, 72.9, 67.1, 63.0, 55.3, 40.5, 39.7, 26.9, 26.3, 19.1, 12.5 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –9.0 ppm. MS (ESI): m/z = 1203.1 $[M + H]^+$.

Data for 14c: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.70 (s, 1 H, NH), 8.16 (s, 1 H, NH), 8.11 (d, J = 7.5 Hz, 1 H, 6$_C$-H), 7.92 (d, J = 7.5 Hz, 2 H, ph), 7.72–7.26 (m, 24 H, ph, 5$_C$-H, and 6$_T$-H), 6.87 (B part of AB syst, J = 9.0 Hz, 4 H, DMT), 6.53 (dd, J = 5.5 and 9.0 Hz, 1 H, 1′$_T$-H), 6.19 (t, J = 6.5 Hz, 1 H, 1′$_C$-H), 5.32 (m, 1 H, 3′$_C$-H), 4.53 (d, J = 5.8 Hz, 1 H, 3′$_T$-H), 4.33–4.19 (m, 2 H, 7′$_T$-H), 4.30 (m, 1 H, 4′$_C$-H), 3.82 (s, 6 H, MeO), 3.75 (m, $J_{H/P} \approx$ 4.0 Hz, 1 H, 5′$_T$-H), 3.73 (s, 1 H, 4′$_T$-H), 3.44 (d, 2 H, 5′$_C$-H), 2.82 (m, 1 H, 2′$_C$-H), 2.44–2.35 (m, 2 H, 2′$_T$-H and 2′$_C$-H), 2.22–2.00 (m, 1 H, 2′$_T$-H), 2.17 (m, 1 H, 6′$_T$-H), 1.87 (br. s, 3 H, Me), 1.41–1.38 (m, 1 H, 6′$_T$-H), 1.12 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 158.7, 150.2, 143.8, 135.4, 135.3, 135.2, 135.1, 134.8, 133.3, 133.2, 132.5, 130.4, 130.3, 130.2, 130.0, 129.1, 129.0, 128.0, 127.8, 127.6, 127.2, 113.3, 111.3, 87.6, 87.5, 87.3, 86.7, 85.2, 85.0, 84.9, 78.8, 77.9, 77.8, 73.9, 66.7, 62.4, 55.3, 40.8, 40.0, 29.7, 27.8, 19.1, 12.7 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –2.9 ppm. MS (ESI): m/z = 1203.1 $[M + H]^+$.

5d, **6d**, and **13d/14d** were separated by reverse-phase chromatography on a Kromasil C_{18}, 7 μm, 100 Å, 250 × 4.6 mm column for analysis or with a 250 × 20 mm preparatory scale column with 25:75 H_2O/acetonitrile. t_r = 17.9 min, 19.0 min, 15.2 min and 21.3 min, respectively. Under these conditions, **14d** could not be isolated in a pure form.

Data for 5d: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.22 (s, 1 H, NH), 8.92 (s, 1 H, NH), 8.69 (2 s, 2 H, 8$_A$-H and 2$_A$-H), 8.07 (2 s, 2 H, 8$_A$-H and 2$_A$-H), 8.04 (m, 2 H, ph), 7.69–7.23 (m, 22 H, ph), 7.17 (br. s, 1 H, 6$_T$-H), 6.79 (B part of an AB syst, J = 8.1 Hz, 4 H, DMT), 6.43 (dd, J = 6.0 and 8.1 Hz, 1 H, 1′$_A$-H), 6.38 (dd, J = 6.0 and 8.7 Hz, 1 H, 1′$_T$-H), 5.20 (m, 1 H, 3′$_A$-H), 4.59 (d, J = 5.4 Hz, 1 H, 3′$_T$-H), 4.49 (br. d, J = 12.3 Hz, $J_{H/P}$ < 1 Hz, 1 H, 5′$_T$-H), 4.30 (m, 1 H, 4′$_A$-H), 4.12–4.05 (m, 2 H, 7′$_T$-H), 3.97 (m, 1 H, 4′$_T$-H), 3.71 (s, 6 H, MeO), 3.40 (m, 2 H, 5′$_A$-H), 3.05 (m, 1 H, 2′$_A$-H), 2.72 (B part of an ABX syst, J = 1.8, 6.0 and 14.4 Hz, 1 H, 2′$_A$-H), 2.24 (A part of an ABX syst, J = 1.8, 6.3 and 13.8 Hz, 1 H, 2′$_T$-H), 2.14 (m, 1 H, 2′$_T$-H), 1.81 (br. s, 3 H, Me), 1.43–1.17 (m, 2 H, 6′$_T$-H), 1.08 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 163.9, 158.7, 151.5, 150.8, 150.1, 144.2, 135.9, 135.8, 135.3, 133.6, 132.8, 132.6, 130.3, 130.0, 128.6, 128.3, 128.1, 127.9, 127.1, 123.5, 113.3, 111.4, 88.0, 87.9, 86.9, 85.3, 85.0, 84.9, 84.5, 80.5, 80.4, 78.6, 72.5, 68.8, 63.0, 60.4, 55.3, 39.6, 37.9, 26.9, 19.1, 12.6 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –9.1 ppm. MS (ESI): m/z = 1248.6 $[M + Na]^+$, 1226.7 $[M + H]^+$.

Data for 6d: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.09 (s, 1 H, NH), 8.73 (2 s, 2 H, 8$_A$-H and 2$_A$-H), 8.12 (2 s, 2 H, 8$_A$-H and 2$_A$-H), 8.02 (m, 2 H, ph), 7.68–7.22 (m, 22 H, ph), 7.09 (br. s, 1 H, 6$_T$-H), 6.79 (B part of an AB syst, J = 8.7 Hz, 4 H, DMT), 6.43 (dd, J = 5.4 and 8.7 Hz, 1 H, 1′$_A$-H), 6.30 (dd, J = 5.7 and 8.7 Hz, 1 H, 1′$_T$-H), 5.24 (t, J = 5.7 Hz, 1 H, 3′$_A$-H), 4.57–4.52 (m, 2 H, 5′$_T$-H and 3′$_T$-H), 4.41–4.29 (m, 2 H, 7′$_T$-H and 4′$_A$-H), 4.23–4.10 (m, 1 H, 7′$_T$-H), 4.00 (m, 1 H, 4′$_T$-H), 3.72 (s, 6 H, MeO), 3.40 (AB part of an ABX syst, J = 3.9, 3.9 and 10.5 Hz, 2 H, 5′$_A$-H), 3.34 (AB part of an ABX syst, J = 3.9, 3.9 and 10.5 Hz, 2 H, 5′$_A$-H), 3.01 (m, 1 H, 2′$_A$-H), 2.69 (B part of an ABX syst, J = 0.9, 5.4 and 13.8 Hz, 1 H, 2′$_A$-H), 2.25 (A part of an ABX syst, J = 1.8, 6.3 and 13.2 Hz, 1 H, 2′$_T$-H), 2.03 (m, 1 H, 2′$_T$-H), 1.82 (br. s, 3 H, Me), 1.62–1.43 (m, 2 H, 6′$_T$-H), 1.07 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 163.8, 158.7, 151.8, 150.4, 149.9, 144.2, 135.9, 135.8, 135.3, 133.5, 132.8, 132.7, 130.3, 130.0, 128.7, 128.2, 128.1, 127.9, 127.1, 123.7, 113.3, 111.6, 88.1, 88.0, 86.8, 86.3, 85.3, 85.2, 84.5, 80.0, 79.3, 79.2, 73.0, 67.2, 67.1, 63.3, 60.4, 55.3, 39.5, 38.8, 26.8, 19.1, 12.5 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = –6.2 ppm. MS (ESI): m/z = 1248.6 $[M + Na]^+$, 1226.7 $[M + H]^+$.

Data for 13d: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.34 (s, 1 H, NH), 8.89 (s, 1 H, NH), 8.81 (2 s, 2 H, 8$_A$-H and 2$_A$-H), 8.19 (2 s, 2 H, 8$_A$-H and 2$_A$-H), 8.06 (m, 2 H, ph), 7.67–7.22 (m, 23 H, ph), 6.78 (B part of an AB syst, J = 9.0 Hz, 4 H, DMT), 6.62 (dd, J = 5.7 and 9.1 Hz, 1 H, 1′$_T$-H), 6.55 (dd, J = 5.4 and 9.3 Hz, 1 H, 1′$_A$-H), 5.21 (t, J = 5.6 Hz, 1 H, 3′$_A$-H), 4.43–4.31 (m, 3 H, 7′$_T$-H, 3′$_T$-H and 4′$_A$-H), 4.15–4.07 (m, 1 H, 7′$_T$-H), 3.76 (s, 1 H, 4′$_T$-H), 3.72 (s, 6 H, MeO), 3.50 (d, J = 11.4 Hz, $J_{H/P}$ < 1 Hz, 1 H, 5′$_T$-H), 3.41 (AB part of an ABX syst, J = 3.3, 3.6 and 10.5 Hz, 2 H, 5′$_A$-H), 3.35 (AB part of an ABX syst, J = 3.3, 3.6 and 10.5 Hz, 2 H, 5′$_A$-H), 2.95 (m, 1 H, 2′$_A$-H), 2.74 (B part of an ABX syst, J = 5.4 and 13.8 Hz, 1 H, 2′$_A$-H), 2.33–2.17 (m, 2 H, 2′$_T$-H and 6′$_T$-H), 2.01–1.94 (m, 4 H, 2′$_T$-H and Me), 1.38 (m, 1 H, 6′$_T$-H), 1.04 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 164.2, 158.7, 152.0, 151.1, 150.1, 144.2, 135.9, 135.3, 135.2, 133.4, 132.8, 132.5, 130.4, 130.0, 128.4, 128.2, 128.1, 128.0, 127.1, 123.7, 113.3, 112.4, 87.7, 87.7, 87.0, 85.5, 85.4, 84.7, 84.2, 79.7, 79.6, 79.3, 74.6, 67.5, 63.4, 60.4, 55.3, 39.9, 39.4, 27.6, 26.9, 19.1, 12.4 ppm.^{31}P NMR (121 MHz, $CDCl_3$): δ = –9.3 ppm. MS (ESI): m/z = 1248.7 $[M + Na]^+$, 1226.6 $[M + H]^+$.

Crystal Data for 9: $C_{23}H_{29.5}N_{4.5}O_{12.5}P$, M = 599.98, monoclinic, $C2$, a = 29.223(6) Å, b = 10.337(2) Å, c = 9.754(2) Å, β = 106.623(5)°, V = 2823.2(10) Å^3, Z = 4 and T = 193(2) K. 6267 reflections (3623 independent, R_{int} = 0.0716) were collected at low temperatures with an oil-coated shock-cooled crystal using a Bruker-AXS CCD 1000 diffractometer with Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97)[24] and all non-hydrogen atoms were refined anisotropically with the least-squares method on F^2.[25] Largest electron density residue: 0.450 e·Å^{-3}; R_1 [for $I > 2\sigma(I)$] = 0.0673 and wR_2 = 0.1661 (all data) with $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{0.5}$. CCDC-614026 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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