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An Adamantane-Based Building Block for DNA Networks

Richa Pathak and Andreas Marx*[a]

Abstract: DNA governs the storage and transfer of genetic information through generations in all living systems with the exception of some viruses. Its physicochemical nature and the Watson–Crick base pairing properties allow molecular constructions at nanometer length, thereby enabling the design of desired structural motifs, which can self-assemble to form large supramolecular arrays and scaffolds. The tailor-made DNAs have been an interesting material for such designed nanoscale constructions. However, the synthesis of specific structures with a desired molecular function is still in its infancy and therefore has to be further explored. To add a new dimension to this approach, we have synthesized a rigid three-way branched adamantane motif, which is capable of forming highly stable DNA networks. The moiety generated could serve as a useful building block for DNA-based nanoconstructions.

Keywords: adamantane · branched DNA · DNA · oligonucleotides · self-assembly

Introduction

The first reports of branched DNA (bDNA) by Seeman in 1982 opened a new era in the field of DNA nanobiotechnology,[1] and since then this area has been continuously explored towards construction of objects for nanobiotechnology. Branched DNA occurs naturally when homologous chromosomes pair up, and the aligned strands of DNA break to crossover and form a Holliday junction. It consists of four DNA strands bound together, and this results in four double-helical arms flanking a branch point.[2] In contrast, synthetic DNA complexes are designed to have fixed branch points consisting of a variable number of arms.[3–10] Numerous branch points have been reported in the literature for various applications. In principle, DNA is a tool for generating complex materials with nanoscale features.[11–18] In this context, DNA-hybrid structures originating from small molecule-DNA hybrids (SMDHs), forming caged dimers possessing three or more DNA strands around a central core, have been generated.[19–20]

Several distinct DNA objects have been synthesized in various geometries such as triangles, pyramids, cubes, and complicated polyhedra.[21–25] Additionally, several reports have appeared in the literature describing the generation of DNA-based nanomechanical devices.[26–29] Despite these novel accomplishments, there is still a need to expand the limited directory of bDNA motifs for the exploration of more versatile and sophisticated arrangements to achieve a greater role of DNA in the macroscopic world.

In recent years, we have reported asymmetrical bDNA by employing a nucleotide analog as a branch point. By varying the protection-group protocols, bDNA constructs were generated, which were further used in the generation of functional DNA networks by the polymerase chain reaction.[30–31] However, to the best of our knowledge there are no reports for the synthesis and utilization of a robust, three-way branched adamantane motif for generation and utilization as bDNA.

Therefore, in our continuing efforts and to add a new dimension to the branch point tool box with yet another very useful variation to our study, we envisioned the synthesis of a rigid, compact, symmetric, and a three-way branched junction as a new bDNA construct. Among the several potential possibilities for a rigid core, the adamantane framework was our structure of choice, as it possesses a T_d symmetric nucleus that represents a strong tetrahedral core, which can be selectively functionalized at the tertiary carbon positions, and it represents the best known examples for rigid and high-order molecular constructions in the literature.[32–35] Adamantane belongs to a class of rigid hydrocarbons processing a high order of symmetry, and is therefore particularly important for use in nanotechnology because the new functionalities could be incorporated at a particular and a

[a] Dr. R. Pathak, Prof. Dr. A. Marx
Department of Chemistry and Konstanz Research School of Chemical Biology University of Konstanz
Universitätsstrasse 10, 78457 Konstanz (Germany)
Fax: (+49) 7531-88-5140
E-mail: Andreas.Marx@uni-konstanz.de

specific intramolecular distance within the adamantane core. In recent years, tetrahedral adamantane tectons possessing nucleosidic sticky ends were synthesized, thereby making use of click chemistry.[36] In this study, we have worked on a new three-way adamantane branch point that allows the attachment of three DNA strands at a fixed distance and fixed interval in a very compact format (Figure 1). We herein present an expeditious synthesis for branched oligonucleotides, in which the trifunctional adamantane linker connects three oligonucleotide strands.

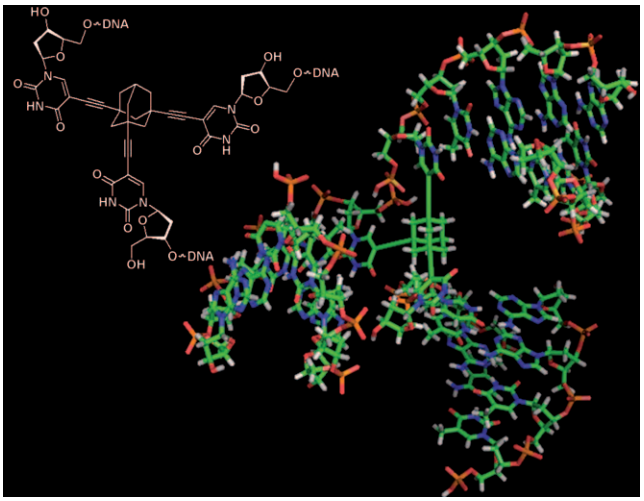


Figure 1. Structure and molecular model depicting DNA duplexes attached to three-way adamantane branch point.

Results and Discussion

To synthesize the three-way adamantane-based bDNA, we first generated 1,3,5-triethynyladamantane **4** from adamantane **1** (Scheme 1), and this required some modifications of reported procedures.[37] Next, we carried out the synthesis of **6** wherein the nucleoside **5** was selectively coupled to only one branch of adamantane **4**. We chose to modify the C5 position in the 2'-deoxyuridine, as such modifications do not significantly interfere with the Watson–Crick base pairings. A palladium-catalyzed cross coupling reaction of the 5′-acetylated nucleoside **5**[38] with **4** afforded compound **6.** During this reaction, we investigated that only very slow addition of the nucleoside **5** to the adamantane derivative **4** leads to exclusive formation of **6**, however, in all other attempts we ended up with mixtures of products as analyzed by TLC. Furthermore, the palladium-catalyzed cross coupling reaction of the adduct **6** with the protected nucleoside **7**[39] was accomplished by following two simultaneous Sonogashira couplings, which yielded the trifunctionalized adamantane building block **8** in good yields. Compound **8** was then treated with 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite in the presence of tetrazole in anhydrous tetrahydrofuran (THF).[40] This reaction gratifyingly yielded the desired phosphoramidite **9** in excellent yield after 20 hours. Having accomplished the synthesis of **9**, we next synthesized the branched oligonucleotide bDNA-**I** in a 3′ to 5′ direction as depicted in Scheme 2. Having synthesized DNA strand **A**, we tried to manually couple the phosphoramidite building block **9** by using syringe techniques described earlier.[41–42] Thus, the column containing DNA was connected to a syringe equipped with the phosphoramidite **9** and an empty syringe. By pushing **9** from one syringe to the other it can react with the free hydroxy group of the DNA. Afterwards, the column was reinstalled for the synthesis of two parallel B branches commencing from the incorporated building block **9** and terminating with a 5′ end.

However, owing to the poor yields obtained by the above procedure, we proceeded with completely automated DNA synthesis and increased the coupling time for the incorporation of **9** to 10 minutes. Gratifyingly, this resulted in a better coupling reaction. When the synthesis was accomplished, the bDNA was cleaved from the solid support and purified by HPLC. The 4,4′-dimethoxytrityl (DMT) group of the last incorporated nucleoside was deprotected manually after RP-HPLC purification. After lyophilisation, the identity of the purified bDNA was confirmed by ESI mass spectrometry.

To investigate whether the branched DNA construct bDNA-**I** was able to form a duplex with complementary DNA, we conducted thermal denaturation studies. The melting temperature (T_m) obtained for the bDNA-**I** was cooperative and comparable with the linear control C-**I** (Figure 2).

a)

Compound	Sequence	UV melting (°C) for duplexes
bDNA-I	(5'ATAGCTAAGACC-/5'ATAGCTAAGACC-) BP(-ATAGCTAAGACC 3')	47
C-I	3' TATCGATTCTGG 5'	
DNA-I	5'ATAGCTAAGACC 3'	50
C-I	3' TATCGATTCTGG 5'	

b)

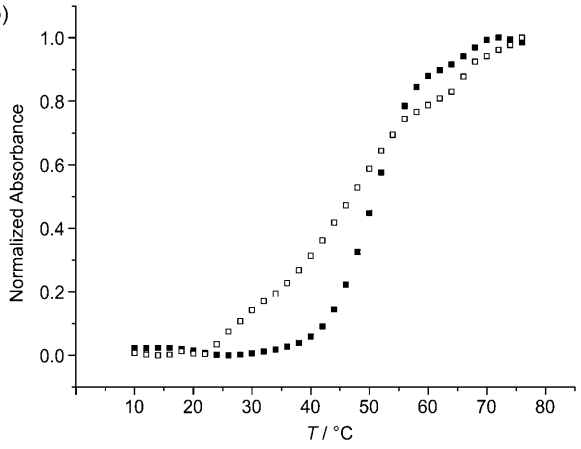
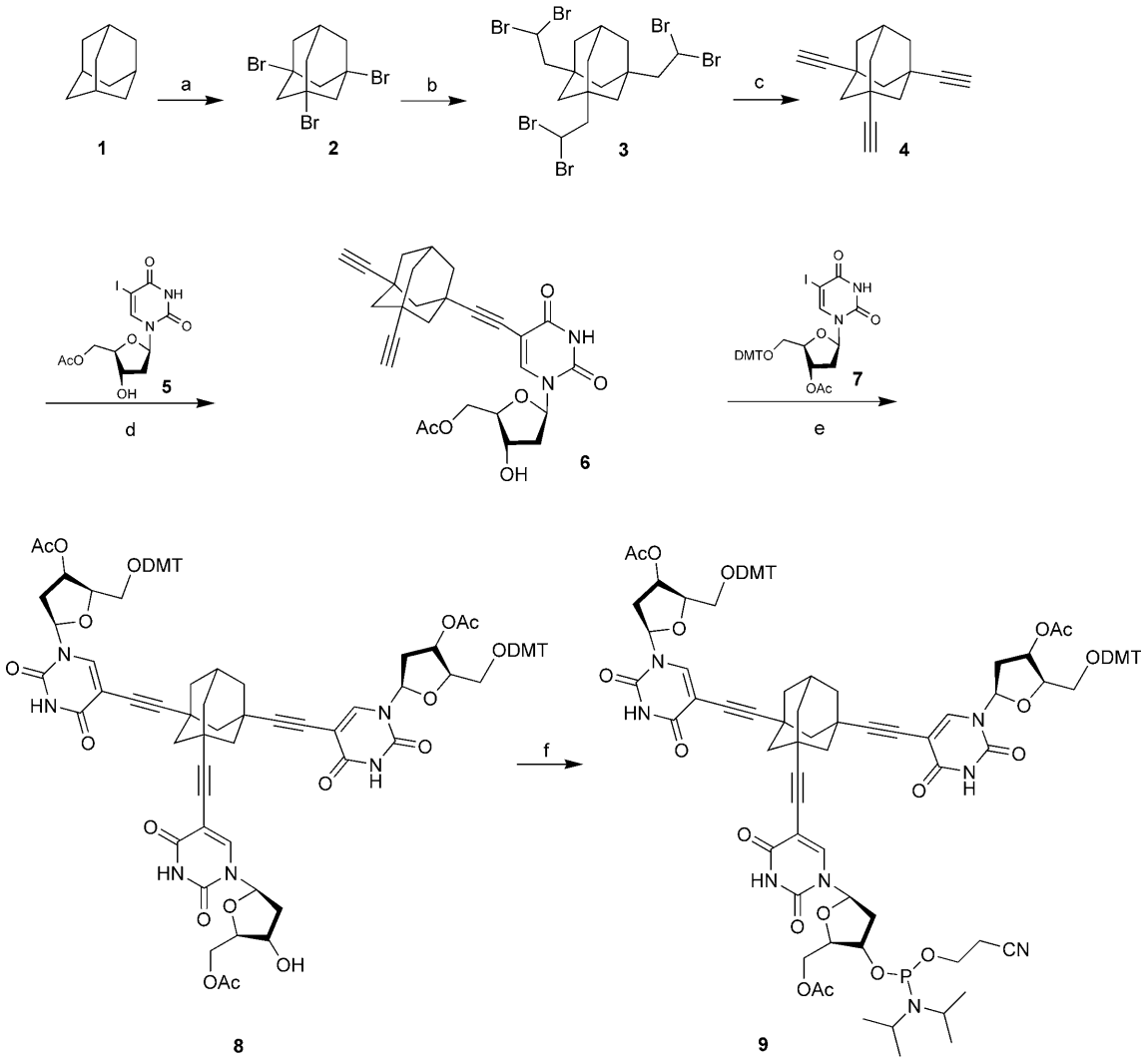


Figure 2. Duplex-formation capability of bDNA-**I** a) Sequences used. b) Melting profile of bDNA-**I** (empty squares) and DNA-**I** (full squares) with complementary strand C-**1**.



Scheme 1. a) Fe, Br_2, 70 °C, 12 h; b) vinyl bromide, anhydrous DMF, Ar, −28 °C, 3 h; c) *t*BuOK, DMSO, 48 h; d) CuI, $[Pd(PPh_3)_4]$, Et_3N, anhydorus THF, Ar, RT, 12 h; e) CuI, $[Pd(PPh_3)_4]$, Et_3N, anhydrous THF, Ar, RT, 4 h; f) tetrazole, 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite, CH_3CN, 0 °C→RT, 20 h.

In the next step to investigate the formation of 3D networks as shown in Figure 3, we synthesized short and self-complimentary monomers bDNA-**II**-**IV** by using a combination of 3′- and 5′-phosphoramidites.[43] We envisioned that such monomers had the potential to form a duplex structure by interacting with the neighbouring monomers, eventually leading to the generation of a bigger DNA network. Thus, we carried out thermal denaturation studies to assert our assumptions. The melting temperature was ascertained by heating the samples from 10 °C to 95 °C and the UV absorbance was monitored at 260 nm. It was observed that melting temperatures for bDNA-**II**, bDNA-**III**, and bDNA-**IV** were drastically elevated in comparison to the control sequences **C**-**II**, **C**-**III**, and **C**-**IV** (Figure 4).

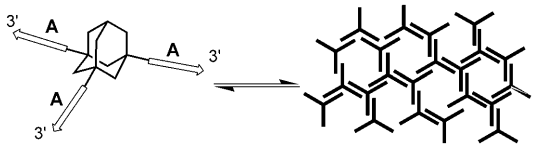
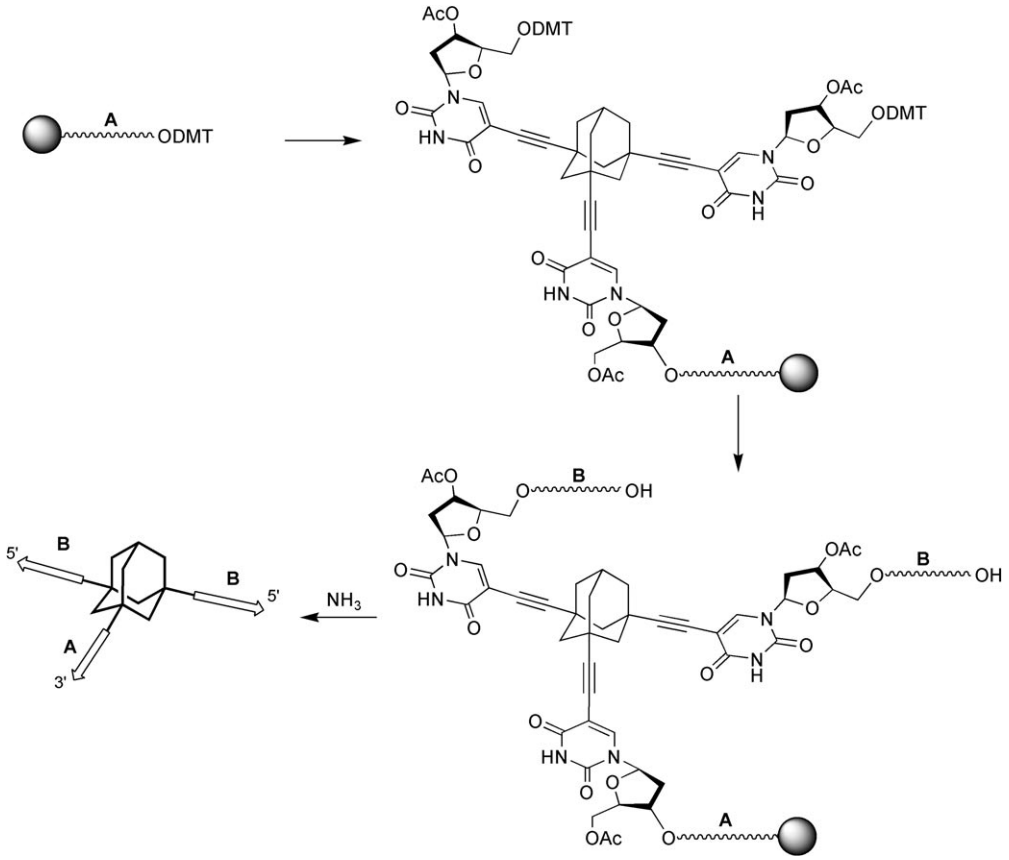


Figure 3. Graphic representation for the formation of DNA networks.

In fact, we were unable to detect any melting behaviour for the short self-complementary sequences, 5′-CG-3′ (**C**-**II**) and 5′-TTAA-3′ (**C**-**III**). Figures 2 and Figure 4 represent the various T_m values for the oligonucleotides **I**–**IV**. On the other hand, it was also noted that slow heating and cooling at 1 °C per minute is more favorable for bDNA-**II**, as no characteristic melting was observed for it at 2 °C per minute. Additionally, reproducibility was also noted for the T_m values by repeating the experiment with the same sample, thus indicating the consistency and stability of DNA network formation. Furthermore, these elevated temperatures assert towards the formation of stable duplexes between the neighbouring bDNA monomers and generation of a larger adamantane-based DNA network. Altogether, it could be



Scheme 2. General strategy for the synthesis of bDNA (A, B = DNA strands).

proposed that multiple interactions are responsible for elevating the melting temperatures of the bDNA-**II**-**IV**. The rigid adamantane core is also providing the desired force needed for the DNA duplex alignment, and thereby leading to the formation of DNA networks.

Conclusions

In conclusion, we have demonstrated a general and robust synthetic protocol for the generation of an adamantane-based building block for DNA networks. The results presented here show that a rigid three-way organic framework can promote DNA network formation. We have shown that two base pairs are sufficient to form networks by self-assembly. These results corroborate earlier findings by using four-way branching points.[44] DNA networks and future tuning of the properties of the networks by chemical manipulations of the branching units might be important constructs for DNA-based nanobiotechnology.

Experimental Section

General

All synthetic reactions were performed under an inert atmosphere. Dry solvents were purchased from Fluka and were stored over molecular sieves and used without further purification. Elemental analysis was carried out by the microanalysis facility at the University of Konstanz. NMR spectra were recorded by using Bruker avance 400 (^{1}H: 400; ^{13}C: 101, ^{31}P: 162 MHz) spectrometers. Chemical shifts are given in parts per million and tetramethyl silane was used as the external standard. Electrospray ionization ion-trap (ESI-IT) mass spectra were recorded by using a Bruker Daltonics esquire 3000+ instrument in positive or negative mode with a flow rate of 3 μL min^{-1}. High-resolution ESI-TOF mass spectra were recorded by using a micrOTOF II (Bruker Daltonics). DNA oligonucleotide synthesis was carried out by using an Applied-Biosystems 392 DNA/RNA synthesizer. Reverse-phase HPLC was performed by using a Prominence HPLC (Shimadzu) instrument equipped with a Nucleosil-100-5 C18 column (250 L 4 mm, Macherey–Nagel). A binary gradient system (triethyl ammonium acetate buffer (0.1 M, pH 7.0/CH_3CN, 25 °C) was used.

*Compound (**3**)*

$AlCl_3$ (0.93 g, 9.0 mmol) was added portionwise to a stirred solution of **2** (2.6 g, 6.9 mmol) in DCM (20 mL) at −28 °C. The mixture was stirred for 15 minutes. This was followed by the continuous purging of vinyl bromide until completion was indicated on the TLC. The reaction mixture was slowly warmed to room temperature and extracted with DCM (200 mL) and 5% HCl in water (150 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude compound **3** was used without further purification.

*Compound (**4**)*

Potassium *tert*-butoxide (1.5 g, 13.3 mmol) was added portionwise to a stirred solution of **3** (1.5 g, 2.2 mmol) in DMSO (15.0 mL) at 0 °C. The mixture was allowed to stir at room temperature for 48 h. The reaction mixture on completion was extracted with DCM (200 mL) and 5% HCl in water (100 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude com-

a)

Compound	Sequence	UV melting (°C) for duplexes/ DNA networks
bDNA-**II**	(3'GC-/ 3' GC-/ 3'GC-) BP	24
C-**II**	5'CG 3'	n.t.*
bDNA-**III**	(3'AATT-/3'AATT-/3'AATT-) BP	43
C-**III**	5'TTAA 3'	n.t.*
bDNA-**IV**	(3'TCCGGA-/3'TCCGGA-/3'TCCGGA-) BP	88
C-**IV**	5'AGGCCT 3'	18

b)

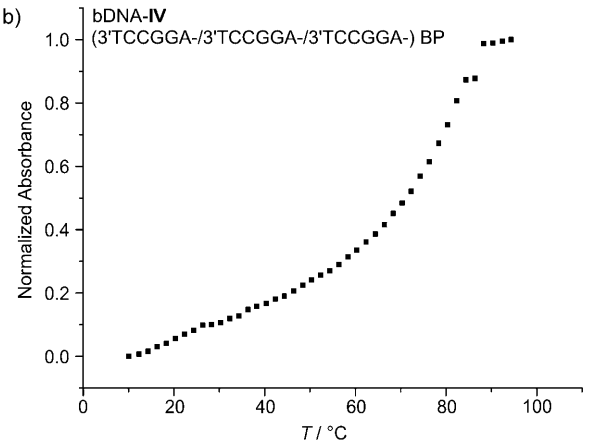


Figure 4. Network-formation capability of self-complementary bDNA a) Sequences used. b) Melting profile of self-complementary bDNA-**IV**. n.t. = no cooperative transition was observed.

pound was purified by means of flash column chromatography on silica gel (0.5% EtOAc in hexane) to give compound **4** (0.28 g, 60%) as a white solid; m.p. 82–85 °C.

*Compound (**6**)*

CuI (0.05 g, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (0.15 g, 0.12 mmol), and anhydrous triethyl amine (1.0 mL, 7.6 mmol) were added to a stirred solution of **4** (0.53 g, 2.5 mmol) in anhydrous THF (5.0 mL). The mixture was allowed to stir for 10 minutes. A solution of **5** (0.67 g, 2.5 mmol) in anhydrous THF (5.0 mL) was added to this mixture over a duration of 15 minutes. The reaction mixture was continuously stirred until completion was indicated on TLC (12 h). It was then evaporated to dryness and diluted with MeOH (15.0 mL), subsequently filtered, and concentrated under reduced pressure. The crude compound was purified by RP-MPLC on a C18 column (CH_3CN/water 1:1) to give compound **6** (0.50 g, 42%) as a yellow solid; m.p. 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69–1.75 (m, 4H, 2 x CH_2), 1.86–1.91 (m, 5H, CH, 2 x CH_2), 1.98 (s, 4H, CH, CH_3), 2.06 (s, 3H, CH, CH_2), 2.10–2.14 (m, 3H, CH_2, 1H of H-2′), 2.39 (ddd, 1H, J = 5.0 Hz, J = 6.3, J = 11.3 Hz, H-2′), 2.71 (d, 1H, J = 4.1 Hz, CHO*H*), 4.07–4.08 (m, 1H, H-5′), 4.25 (dd, 1H, J = 3.0 Hz, J = 12.3 Hz, H-5′), 4.31–4.35 (m, 2H, H-4′, H-3′), 6.17 (t, 1H, J = 6.1 Hz, H-1′), 8.01 ppm (s, 1H, =CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.2, 21.1, 21.2, 27.8, 29.8, 30.7, 40.3, 40.4, 46.1, 46.2, 60.5, 63.6, 68.4, 71.1, 84.6, 85.7, 89.9, 100.2, 100.6, 141.3, 149.4, 161.6, 170.7, 171.3 ppm; (ESIMS): m/z: calcd for $C_{27}H_{28}N_2O_6$: 477.1 $[M+H]^+$; found: 499.1 $[M+Na]^+$.

*Compound (**8**)*

7 (0.471 g, 0.7 mmol), CuI (0.024 g, 0.12 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.074 g, 0.06 mmol) were added to a stirred solution of **6** (0.153 g, 0.32 mmol) in anhydrous THF (10.0 mL) and the mixture was allowed to stir for 10 minutes. This was followed by the addition of anhydrous triethyl amine (0.4 mL, 3.2 mmol). The reaction mixture was continuously stirred until completion was indicated on TLC (12 h). It was then evaporated to dryness and was further diluted with MeOH (20 mL). Subsequently the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The crude product was purified by RP-MPLC on a C18 column (CH_3CN/water 1:1) to give compound **8** (0.415 g, 76%) as a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.82 (m, 1H, CH), 2.05–2.07 (m, 21H, 6 x CH_2, 3 x CH_3), 2.28–2.37 (m, 2H, H-2′), 2.50–2.59 (m, 4H, 2 x H-2′), 2.8 (brs, 1H, CHO*H*), 3.37 (dd, 2H, J = 3.3 Hz, J = 10.7 Hz, H-5′), 3.45 (dd, 2H, J = 2.6 Hz, J = 10.6 Hz, H-5′), 3.81 (s, 12H, OCH_3), 4.12–4.15 (m, 1H, H-3′), 4.18–4.19 (m, 2H, H-4′, H-3′), 4.27 (dd, 1H, J = 3.5 Hz, J = 12.1 Hz, H-5′), 4.34 (dd, 1H, J = 4.2 Hz, J = 12.2 Hz, H-5′), 4.44–4.48 (m, 1H, H-3′), 5.43–5.44 (m, 2H, 2 x H-4′), 6.27–6.32 (m, 3H, 3 x H-1′), 6.93 (d, 8H, J = 8.8 Hz, ArH), 7.26–7.30 (m, 2H, ArH), 7.35–7.39 (m, 4H, ArH), 7.40–7.44 (m, 8H, ArH), 7.54–7.56 (m, 4H, ArH), 7.88 (s, 1H, =CH), 8.08 ppm (s, 2H, = CH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 20.0, 20.3, 27.8, 30.2, 30.4, 37.9, 40.0, 45.1, 45.5, 54.7, 63.4, 63.5, 70.8, 71.7, 72.3, 74.8, 84.2, 84.7, 84.8, 85.3, 86.7, 98.7, 98.9, 99.8, 100.3, 113.2, 113.3, 126.9, 128.0, 128.1, 130.0, 130.1, 135.7, 135.8, 141.4, 144.8, 149.4, 149.5, 158.6, 158.7, 161.0, 161.1, 169.8, 169.9 ppm; (ESIMS): m/z (%): 1616.9 $[M-1]^-$. HR-ESIMS: m/z: calcd for $C_{91}H_{88}N_6O_{22}$: 1616.5952; found: 1616.7298.

*Compound (**9**)*

Tetrazole (12 μL, 2.0 mmol) was added to a stirred solution of **8** (0.11 g, 1.0 mmol) in anhydrous THF (5.0 mL) at 0 °C under an argon atmosphere and was stirred for 5 minutes. Subsequently 2-cyanoethyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite (43 μL, 2.0 mmol) was added and the reaction mixture was continued to stir for 20 h or until completion was evident from TLC. The reaction mixture was then diluted with a saturated solution of $NaHCO_3$ (30 mL) and extracted with EtOAc (40 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under a nitrogen atmosphere under reduced pressure. The crude compound was purified by means of flash column chromatography on silica gel (40% EtOAc in hexane) to give compound **9** (0.12 g, 91%) as a colorless oil; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 148.6, 148.8 ppm; mass (ESIMS): m/z: 1816.1 $[M-1]^-$.

General Procedure for the Synthesis of bDNA

The synthesis of bDNA oligonucleotides was performed by using an Applied Biosystems 392 DNA synthesizer with a 3′-CPG support (1000 Å) and commercially available 3′-*O*-2-CE phosphoramidites (CE = cyanoethyl) on a 0.2 mmol scale. After insertion of branch point **9**, DNA synthesis was continued and standard coupling conditions were utilized in the case of the 3′- and 5′-CE phosphoramidites, whereas for the insertion of branch point **9**, the coupling times were extended to 10 minutes by using **9** (0.1 M) in CH_3CN. The extension of each branch was terminated by first cleaving the respective DMT group and subsequently passing capping mixtures A (acetic anhydride/pyridine/THF) and B (*N*-methylimdidazole/pyridine/THF) over the solid support for 3 × 15 s. At the end of the synthesis, the DMT group was retained ("trityl ON"), which allowed failed sequences to be removed by means of reverse-phase HPLC with a binary gradient of CH_3CN in triethylammonium acetate buffer (pH 7.0). The desired bDNA containing the DMT group was collected, deprotected by using 80% AcOH, purified by using means of reverse-phase HPLC with a binary gradient of CH_3CN in triethylammonium acetate buffer (pH 7.0), and characterized by using ESIMS.

UV-melting analysis

UV-melting curves were aquired on a Cary 100 Bio spectrophotometer. The heating and cooling curves were detected at 260 nm at the gradients of 2 °C/min^{-1} or 1 °C/min^{-1}. The melting temperatures were determined from the extremum of the first derivative of 75 or 95-point curves.

ESI measurements

The purified bDNA molecules and oligonucleotide templates (50–100 pmol) were dissolved in a solution of 2-propanol (20%) containing NEt_3 (1%).[45] The mass measurements were carried out by using an Esquire 3000+ (Bruker) instrument and nitrogen was used as the nebulizing

gas (12 psi) at 300 °C. The samples were injected into the system with the aid of a syringe pump (180 $\mu L\,h^{-1}$).

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[1] N. C. Seeman, *J. Theor. Biol.* **1982**, *99*, 237.
[2] M. F. White, M. J. E. Giraud-Panis, J. R. G. Polher, D. M. J. Lilley, *J. Mol. Biol.* **1997**, *269*, 647.
[3] N. C. Seeman, *Chem. Intell.* **1995**, *1*, 38.
[4] R.-I. Ma, N. R. Kallenbach, R. D. Sheardy, M. L. Petrillo, N. C. Seeman, *Nucleic Acids Res.* **1986**, *14*, 9745.
[5] Y. Wang, J. E. Mueller, B. Kemper, N. C. Seeman, *Biochemistry* **1991**, *30*, 5667.
[6] N. C. Seeman, *Angew. Chem.* **1998**, *110*, 3408; *Angew. Chem. Int. Ed.* **1998**, *37*, 3220.
[7] D. Liu, S. H. Park, J. H. Reif, T. H. LaBean, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 717.
[8] N. C. Seeman, *Nature* **2003**, *421*, 427.
[9] N. C. Seeman, *Nano Lett.* **2001**, *1*, 22.
[10] E. Winfree, F. Liu, L. A. Wenzler, N. C. Seeman, *Nature* **1998**, *394*, 539.
[11] N. C. Seeman, *Annu. Rev. Biochem.* **2010**, *79*, 65.
[12] K. V. Gothelf, A. Thomsen, M. Nielsen, E. Clo, R. S. Brown, *J. Am. Chem. Soc.* **2004**, *126*, 1044.
[13] S. A. Ivanov, Eugene, M. Volkov, T. S. Oretskaya, S. Mueller, *Tetrahedron* **2004**, *60*, 9273.
[14] L. H. Eckardt, K. Naumann, W. M. Pankau, M. Rein, M. Schweitzer, N. Windhab, G. von Kiedrowski, *Nature* **2002**, *420*, 286.
[15] T. Horn, C.-A. Chang, M. S. Uredea, *Nucleic Acids Res.* **1997**, *25*, 4842.
[16] M. S. Shchepinov, I. A. Udalova, A. J. Bridgman, E. M. Southern, *Nucleic Acids Res.* **1997**, *25*, 4447.
[17] R. S. Braich, M. J. Damha, *Bioconjugate Chem.* **1997**, *8*, 370.
[18] M. Endo, K. Hidaka, T. Kato, K. Namba, H. Sugiyama, *J. Am. Chem. Soc.* **2009**, *131*, 15570.
[19] B. R. Stepp, J. M. Gibbs-Davis, D. L. F. Koh, S. T. Nguyen, *J. Am. Chem. Soc.* **2008**, *130*, 9628.
[20] M. Scheffler, A. Dorenbeck, S. Jordan, M. Wüstefeld, G. von Kiedrowski, *Angew. Chem.* **1999**, *111*, 3513; *Angew. Chem. Int. Ed.* **1999**, *38*, 3311.
[21] a) J. Chen, N. C. Seeman, *Nature* **1991**, *350*, 631; b) Y. Zhang, N. Seeman, *J. Am. Chem. Soc.* **1994**, *116*, 1661.
[22] X. Yang, L. Wenzler, J. Qi, X. Li, N. Seeman, *J. Am. Chem. Soc.* **1998**, *120*, 9779.
[23] W. M. Shih, J. D. Quispe, G. F. Joyce, *Nature* **2004**, *427*, 618.
[24] C. Erben, R. Goodman, A. Tuberfield, *J. Am. Chem. Soc.* **2007**, *129*, 6992.
[25] T. Omabegho, R. Sha, N. C. Seeman, *Science* **2009**, *324*, 67.
[26] A. Rich, A. Nordheim, A. H. Wang, *Annu. Rev. Biochem.* **1984**, *53*, 791.
[27] C. Mao, W. Sun, Z. Shen, N. C. Seeman, *Nature* **1999**, *397*, 144.
[28] S. Modi, M. G. Swetha, D. Goswami, G. Gupta, S. Mayor, Y. Krishnan, *Nat. Nanotechnol.* **2009**, *4*, 325.
[29] X. Hou, W. Guo, F. Xia, F. Q. Nie, H. Dong, Y. Tian, L. Wen, L. Wang, L. Cao, Y. Yang, J. Xue, Y. Song, Y. Wang, D. Liu, L. Jiang, *J. Am. Chem. Soc.* **2009**, *131*, 7800.
[30] a) S. Keller, J. Wang, M. Chandra, R. Berger, A. Marx, *J. Am. Chem. Soc.* **2008**, *130*, 13188; b) M. Chandra, S. Keller, C. Gloeckner, B. Bornemann, A. Marx, *Chem. Eur. J.* **2007**, *13*, 3558.
[31] M. Chandra, Y. Luo, S. Keller, A. Marx, *Tetrahedron* **2007**, *63*, 8576.
[32] Q. Li, C. Jin, P. A. Petukhov, A. V. Rukavishnikov, T. O. Zaikova, A. Phadke, D. H. LaMunyon, M. D. Lee, J. F. W. Keana, *J. Org. Chem.* **2004**, *69*, 1010.
[33] Q. Li, A. V. Rukavishnikov, P. A. Petukhov, T. O. Zaikova, C. Jin, J. F. W. Keana, *J. Org. Chem.* **2003**, *68*, 4862.
[34] P. Brunet, E. Demers, T. Maris, G. D. Enright, J. D. West, *Angew. Chem.* **2003**, *115*, 5461; *Angew. Chem. Int. Ed.* **2003**, *42*, 5303.
[35] D. Laliberté, T. Maris, J. D. Wuest, *Can. J. Chem.* **2004**, *82*, 386.
[36] O. Plietzsch, C. I. Schilling, M. Tolev, M. Nieger, C. Richert, T. Muller, S. Bräse, *Org. Biomol. Chem.* **2009**, *7*, 4734.
[37] A. A. Malik, T. G. Archibald, K. Baum, M. R. Unroe, *J. Polym. Sci. Part A* **1992**, *30*, 1747.
[38] G. X. He, N. Bischofberger, *Nucleosides Nucleotides* **1997**, *16*, 257.
[39] J. A. Montgomery, H. J. Thomas, *J. Med. Chem.* **1967**, *10*, 1163.
[40] H. Dougan, J. B. Hobbs, J. I. Weitz, D. M. Lyster, *Nucleic Acids Res.* **1997**, *25*, 2897.
[41] R. B. Jagt, R. F. Gomez-Biagi, M. Nitz, *Angew. Chem.* **2009**, *121*, 2029; *Angew. Chem. Int. Ed.* **2009**, *48*, 1995.
[42] A. V. Lebedev, D. Combs, R. I. Hogrefe, *Bioconjugate Chem.* **2007**, *18*, 1530.
[43] T. Wagner, W. Pfleiderer, *Helv. Chim. Acta* **2000**, *83*, 2023.
[44] M. Meng, C. Ahlborn, M. Bauer, O. Plietzsch, S. A. Soomro, A. Singh, T. Muller, W. Wenzel, S. Bräse, C. Richert, *ChemBioChem* **2009**, *10*, 1335.
[45] G. De Bellis, G. Salani, G. Battaglia, P. Pietta, E. Rosti, P. Mauril, *Rapid Commun. Mass Spectrom.* **2000**, *14*, 243.

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