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A rapid efficient microwave-assisted synthesis of a 3′,5′-pentathymidine by copper(I)-catalyzed [3+2] cycloaddition

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ABSTRACT

Starting from 5′-*O*-tosylthymidine, sequential azidation and Cu-catalyzed [3+2] azide–alkyne 1,3-dipolar cycloaddition led to the formation of a 3′,5′-pentathymidine in high yield. The whole process needed only work-up/precipitation steps and was completed within just 18 min, thanks to microwave activation.
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1. Introduction

Synthetic oligonucleotides play pivotal roles in the design of molecular tools used in genomic research and biotechnology.[1] Antisense and triple helix therapies are two major applications of these oligomeric structures.[2] Oligonucleotide analogues have thus attracted a lot of interest and more especially those harboring a non-phosphodiester backbone.[3] However, nucleoside chemistry, made extremely delicate because of numerous reactive sites, requires appropriate and often cumbersome protection/deprotection steps. Thus, reduction in their number constitutes an attractive challenge. In this way, the Huisgen 1,3-dipolar cycloaddition[4] between azides and alkynes, performed by the recently discovered copper(I) catalysis[5] appears as a promising way to generate oligomers[6] and particularly non-natural oligodeoxyribonucleotides, which can resist chemical or enzymatic depolymerization. Moreover the 100% regioselective formation of 1,4-disubstituted-1,2,3-triazole conserves the directional character of DNA strands. At last, microwave activation, associated to Cu-catalyzed [3+2] azide–alkyne cycloaddition, dramatically decreases reaction time.[7]

2. Results and discussion

In conjunction with our efforts to generate rapidly and efficiently oligonucleosides,[8] we were especially interested in a new strategy beginning with the selective 5′-O-tosylation of thymidine.

The tosyl group is a good compromise; it can be used as a protective group and it can easily generate azido-functionalized compounds. Thus, tosylated thymidine was transformed into 5′-azidothymidine and, in a separate reaction, 3′-hydroxyl was alkylated by an alkynylbromide, then these two precursors were conjugated using the [3+2] cycloaddition reaction.

Selective tosylation of the primary hydroxyl group of thymidine gave the already known product **1**.[9] Then azidation of **1** using 15 equiv of sodium azide in DMF produced in 91% yield precursor **2** after 1 min microwave activation (120 °C, 300 W).[10] Alkyne **3** was obtained by regioselective 3′-O-alkylation using Chattopadhyaya's two-step method[11] under microwave irradiation. During the first step compound **1** was activated (40 °C, 200 W, 3 min) with 2.5 equiv of NaH in THF then in the second step 2.5 equiv of propargyl bromide was added and the mixture was irradiated 3 min. The reaction produced compound **3** in 96% yield (Scheme 1).

Derivatives **2** and **3** were then coupled using copper(I)-catalyzed cycloaddition in order to obtain 1,4 dithymidine-substituted-1,2,3-triazole **4** (Scheme 2). Optimization of this reaction has been described in a previous paper.[8] Alkyne and azide precursors were suspended in a 1:1 mixture of water and ethanol, together with catalyst and sodium ascorbate. After 3 min of irradiation, treatment with THF gave dimer **4** in excellent yield (92%). Despite of a TLC analysis, which unveiled traces of remaining compound **3**, the reaction mixture containing dimer **4** was directly used in following steps.

Tosyldithymidine (**4**) was then converted into 'azido' dimer **5** by using the same conditions as for synthesis of compound **2**. In this

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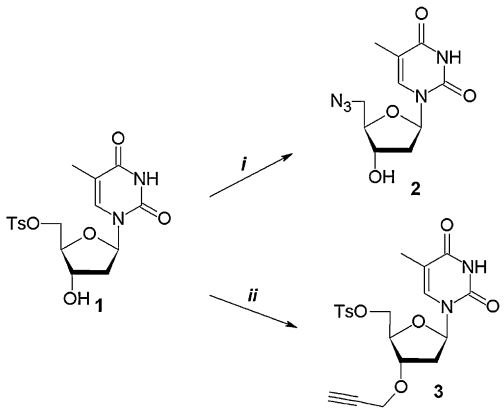


Scheme 1. Preparation of precursors **2** and **3**. Reagents and conditions: (i) NaN_3, DMF, MW (120 °C, 300 W, 1 min); (ii) (1) NaH, THF, MW (40 °C, 200 W, 3 min), (2) propargyl bromide, MW (40 °C, 200 W, 3 min).

case 2 min (120 °C, 300 W) of activation were necessary for the total disappearance of the starting tosylated compound. Treatment with THF led to the desired product in 94% yield.

A click reaction between compounds **5** and **3** using the same reagents and activation time as for dimer **4** gave—without purification—trimer **6** in quantitative yield. These two steps of azidation and [3+2] cycloaddition were repeated under identical conditions and provided 'azido' trimer **7** (80%) and tetramer **8**.[12] Compound **8** precipitated during the reaction. After filtration and washing with THF, pure tosyltetramer was isolated in 72% yield. Azidation of compound **8** in DMF gave 'azido' tetramer **9** in 93% yield after extraction with THF. Since tetramer is insoluble in H_2O/EtOH, CuI/DIPEA/DMF click system[8,13] was used for [3+2] cycloaddition and gave pentamer **10** after 3 min of microwave activation (120 °C, 300 W). After precipitation with water and filtration, pure pentathymidine was isolated in 99% yield.

Overall process combining the five steps from the first to the last cycloaddition reaction totaled only 18 min; pure pentamer **10** was synthesized in 46% overall yield from **2**.

Structures of isolated products **3–10** were determined by ^1H, ^{13}C, ^1H–^1H COSY, ^{13}C–^1H HMQC, and ^{13}C–^1H HMBC measurements (after purification of each product by preparative chromatography, except for compounds **8–10**).

3. Conclusion

In conclusion, a new, fast, and efficient procedure using alternating azidation and click chemistry was developed for tetrathymidine analogue synthesis. Microwave activation was used throughout and provided **10** in good yield. Continued advancement of this strategy could find interesting applications in solid phase synthesis to generate a new family of oligonucleotide analogues.

4. Experimental

4.1. General methods

All the solvents and chemicals were commercially available and, unless otherwise stated, were used as received. Reactions were monitored by thin layer chromatography (TLC) on precoated 0.2 mm silica gel 60 F_{254} (Merck) plates and visualized in several ways: with an ultraviolet light source at 254 nm, by spraying with sulfuric acid (6 N), and heating to 200 °C. Microwave irradiations were performed by the means of an Ethos 1600 MicroSynth reactor from Milestone. Temperature was measured with a fiber optic thermometer (ATC-FO)/Ethos. ^1H NMR spectra were recorded at 400.13 MHz with a Brüker DPX spectrometer. Chemical shifts (δ) are expressed in parts per million with Me_4Si as an internal standard (δ=0). Data are reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, and br, broad), coupling constants (Hz), and assignment. Melting points (mp) were determined with an Electrothermal Digital Melting Point Apparatus IA9000 series. IR spectra were recorded on a Perkin–Elmer 1310 grating spectrophotometer and are reported in wave number (cm^{-1}).

4.2. Synthesis

4.2.1. Synthesis of precursor *2*

Compound **1** (100 mg, 0.38 mmol) was treated with 15 equiv of sodium azide (372 mg, 5.7 mmol) in DMF (8 mL) and was activated by microwave for 1 min (120 °C, 300 W). Compound **2** gave intense purple spots after spraying first PPh_3/Et_2O then ninhydrin and heating. The mixture was evaporated and purified by flash chromatography with a $CHCl_3$/MeOH elution gradient. Pure product was obtained as a white solid in 91% yield; mp=164–166 °C; IR: ν_{max} (cm^{-1})=3366, 2104, 1690, 1645. ^1H NMR (DMSO-d_6) *thymine*: 11.32 (br s, 1H, N–H), 7.49 (s, 1H, H_6), 1.79 (s, 3H, CH_3); *ose*: 6.20 (t, 1H, J=7 Hz, $H_{1'}$), 5.41 (d, 1H, J=3.7 Hz, OH), 4.19 (m, 1H, $H_{3'}$), 3.85 (br dd, 1H, J=5.2, 8.9 Hz, $H_{4'}$), 3.58 (dd, 1H, J=5.3, 13.0 Hz, $H_{5'a}$), 3.53 (dd, 1H, J=5.3, 13.0 Hz, $H_{5'b}$), 2.25 (ddd, 1H, J=6.5, 7, 13.6 Hz, $H_{2'a}$), 2.09 (ddd, 1H, J=3.7, 6.4, 13.5 Hz, $H_{2'b}$). ^{13}C NMR (DMSO-d_6): 163.6 (C4), 150.5 (C2), 136.0 (C6), 109.7 (C5), 84.5 (C4′), 83.8 (C1′), 70.6 (C3′), 51.6 (C5′), 38.0 (C2′), 12.0 (CH_3); MS (IS) m/z=268.1 ($M+H^+$), 290.1 ($M+Na^+$), 306.1 ($M+K^+$), 535.3 (MH^+M), 557.2 (MNa^+M), 824.3 (M_3Na^+).

4.2.2. Synthesis of precursor *3*

To a solution of compound **1** (1.011 g, 2.55 mmol) in dry THF (15 mL) was added 2.5 equiv of NaH (60%, 255 mg, 6.38 mmol) and the mixture was activated by microwave irradiation (40 °C, 200 W, 3 min). Propargyl bromide of 2.5 equiv (80% in toluene, 690 μL, 6.38 mmol) was then added and the mixture was activated by microwave irradiation (40 °C, 200 W, 3 min). After work-up (NH_4Cl/H_2O) and purification by chromatography (chloroform as eluent) **3** was recovered in 96% yield (1.107 g); mp=40–41 °C; IR: ν_{max} (cm^{-1})=3040, 2359, 1688, 1361. ^1H NMR (DMSO-d_6) *thymine*: 11.34 (br s, 1H, N–H), 7.41 (d, 1H, $J_{H_6,\,CH_3}$ = 0.8 Hz, H_6), 1.77 (s, 3H, CH_3); *ose*: 6.08 (dd, 1H, J=6.5, 7.7 Hz, $H_{1'}$), 4.27 (dd, 1H, J=3.6, 10.9 Hz, $H_{5'a}$), 4.25 (m, 1H, $H_{3'}$), 4.21 (dd, 1H, J=5.5, 10.9 Hz, $H_{5'b}$), 4.08 (m, 1H, $H_{4'}$), 2.29 (ddd, 1H, J=6.3, 7.7, 14.2 Hz, $H_{2'a}$), 2.22 (ddd, 1H, J=6.3, 6.5, 14.2 Hz, $H_{2'b}$); *tosyl*: 7.79 (d, 2H, J=8.2 Hz, H_2, H_6), 7.48 (d, 2H, J=8.2 Hz, H_3, H_5), 2.40 (s, 3H, CH_3); *propargyl*: 4.18 (d, 2H, J=2.3 Hz, CH_2), 3.47 (t, 1H, J=2.3 Hz, C–H). ^{13}C NMR (DMSO-d_6): 163.5 (C_4), 150.3 (C_2), 135.7 (C_6), 109.5 (C_5), 84.3 ($C_{1'}$), 80.6 ($C_{4'}$), 77.8 ($C_{3'}$), 69.9 ($C_{5'}$), 35.3 ($C_{2'}$), 11.9 (CH_3); *tosyl*: 145.1 (C_4), 131.2 (C_1), 130.1 (C_3, C_5), 127.5 (C_2, C_6), 21.0 (CH_3); *propargyl*: 79.9 (C), 77.4 (CH), 56.2 (CH_2); MS (IS) m/z=435.2 ($M+H^+$), 457.2 ($M+Na^+$), 891.3 (MNa^+M).

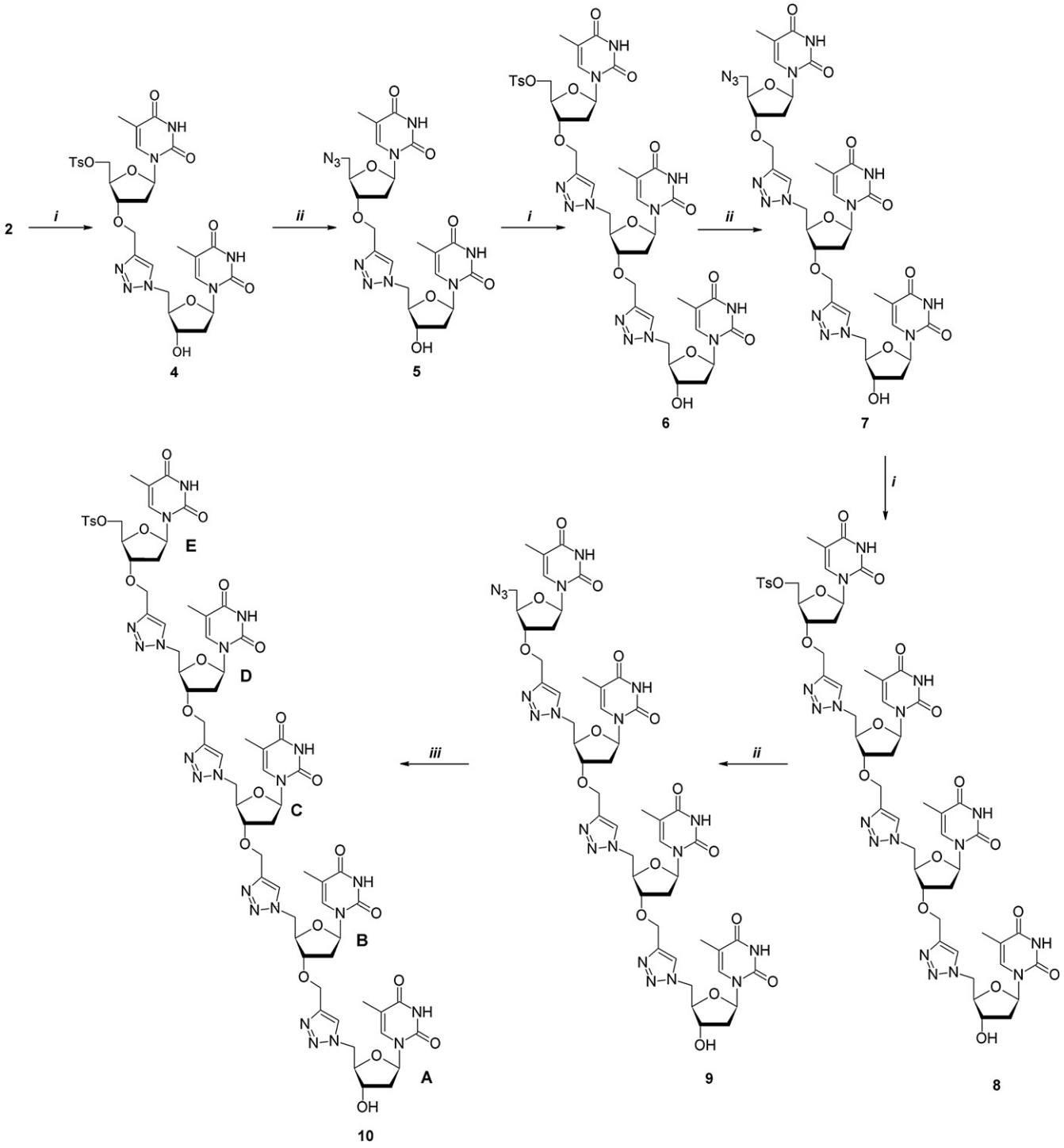
4.3. General procedure for click chemistry

Compound **2** (317 mg, 1.19 mmol), **3** (490 mg, 1.13 mmol), sodium ascorbate (680 μL, 1 M, 0.6 equiv), and copper sulfate pentahydrate (17 mg, 0.06 equiv) were suspended in a 1:1 mixture of water and ethanol (4 mL each) in a 25 mL bicol (open reaction vessel). The mixture was then irradiated for 3 min at 80 °C, using an irradiation power of 300 W. After work-up (THF), the crude residue was concentrated in vacuo and product **4** was recovered as a white solid (92%).

4.4. Compounds 4–10

4.4.1. Compound *4*

Isolation by preparative chromatography: $CHCl_3$/EtOH (8:2). ^1H NMR (DMSO-d_6) *thymines*: 11.33 (s, 1H, NH), 11.30 (s, 1H, NH), 7.40 (d, 1H, J=0.8 Hz, H_{6B}), 7.34 (d, 1H, J=0.9 Hz, H_{6A}), 1.79 (d, 3H,



Scheme 2. Synthesis of pentathymidine **10**. Reagents and conditions: (i) **3**, $CuSO_4$ (0.06 equiv), Na ascorbate (0.6 equiv), H_2O/EtOH (1:1), MW (80 °C, 300 W, 3 min); (ii) NaN_3, DMF, MW (120 °C, 300 W, 2 min); (iii) **3**, CuI (1 equiv), DIPEA (3 equiv), DMF, MW (120 °C, 300 W, 3 min).

J=0.5 Hz, $_{5A}CH_3$), 1.77 (d, 3H, J=0.5 Hz, $_{5B}CH_3$); *oses*: 6.16 (br t, 1H, J=7.0 Hz, $H_{1'A}$), 6.09 (br t, 1H, J=7.5 Hz, $H_{1'B}$), 5.50 (d, 1H, J=4.4 Hz, OH), 4.71 (dd, 1H, J=4.4, 14.2 Hz, $H_{5'A}$), 4.61 (dd, 1H, J=7.6, 14.2 Hz, $H_{5'A}$), 4.28 (dd, 1H, J=3.4, 10.7 Hz, $H_{5'B}$), 4.28 (m, 1H, $H_{3'A}$), 4.22 (dd, 1H, J=5.5, 10.9 Hz, $H_{5'B}$), 4.17 (br ddd, 1H, J=3.0, 5.7 Hz, $H_{3'B}$), 4.09 (m, 1H, $H_{4'B}$), 4.07 (br dd, 1H, J=4.2, 7.6 Hz, $H_{4'A}$), 2.23 (m, 2H, $H_{2'B}$), 2.17 (br dd, 1H, J=6.7, 13.7 Hz, $H_{2'A}$), 2.10 (ddd, 1H, J=3.9, 6.4, 13.5 Hz, $H_{2'A}$); *linker*: 8.08 (s, 1H, $H_{triazol}$), 4.54 (d, 1H, J=12.2 Hz, CH_2), 4.51 (d, 1H, J=12.1 Hz, CH_2); *tosyl*: 7.79 (d, 2H, J=8.3 Hz, H_2, H_6), 7.47 (d, 2H, J=8.2 Hz, H_3, H_5), 2.40 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) *thymines*: 163.6 (C_{4A}, C_{4B}), 150.4 (C_{2A} or C_{2B}), 150.3 (C_{2A} or C_{2B}), 136.1 (C_{6A}), 135.8 (C_{6B}), 109.8 (C_{5A}, C_{5B}), 12.1 ($_{5A}CH_3$ or $_{5B}CH3$), 12.0 ($_{5A}CH_3$ or $_{5B}CH_3$); *oses*: 84.3 ($C_{1'B}$), 84.0 ($C_{1'A}$ or $C_{4'A}$), 83.9 ($C_{1'A}$ or $C_{4'A}$), 80.8 ($C_{4'B}$), 78.3 ($C_{3'B}$), 70.7 ($C_{3'A}$), 70.1 ($C_{5'B}$), 51.2 ($C_{5'A}$), 37.9 ($C_{2'A}$), 35.6 ($C_{2'B}$); *linker*: 143.6 ($C_{triazol}$), 124.7 ($CH_{triazol}$), 62.1 (CH_2); *tosyl*: 145.2 (C_4), 132.1 (C_1), 130.2 (C_3, C_5), 127.6 (C_2, C_6), 21.1 (CH_3); mp=153–155 °C; IR (cm^{-1}): ν_{max}=3651, 3550, 1691, 1363, 1176; MS (IS) m/z=724.3 ($M+Na^+$).

4.4.2. Compound **5**

Isolation by preparative chromatography: $CHCl_3$/EtOH (8:2). ^1H NMR (DMSO-d_6) *thymines*: 11.30 (s, 2H, 2NH), 7.44 (br s, 1H, H_{6B}),

7.29 (br s, 1H, H_{6A}), 1.78 (br s, 6H, $_{5A}CH_3$, $_{5B}CH_3$); *oses*: 6.20 (br t, 1H, J=7.3 Hz, $H_{1'A}$), 6.18 (br t, 1H, J=8.4 Hz, $H_{1'B}$), 5.50 (d, 1H, J=4.4 Hz, OH), 4.71 (dd, 1H, J=4.4, 14.3 Hz, $H_{5'A}$), 4.61 (dd, 1H, J=7.6, 14.4 Hz, $H_{5'A}$), 4.28 (br ddd, J=3.6, 6.6 Hz, $H_{3'A}$), 4.15 (br ddd, 1H, J=2.5, 5.3 Hz, $H_{3'B}$), 4.07 (br dd, 1H, J=4.0, 7.6 Hz, $H_{4'A}$), 4.03 (m, 1H, $H_{4'B}$), 3.60 (dd, 1H, J=6.2, 13.1 Hz, $H_{5'B}$), 3.55 (dd, 1H, J=4.6, 13.2 Hz, $H_{5'B}$), 2.22 (m, 2H, $H_{2'B}$), 2.16 (br dd, 1H, J=6.8, 13.7 Hz, $H_{2'A}$), 2.07 (ddd, 1H, J=3.8, 6.4, 13.4 Hz, $H_{2'A}$); *linker*: 8.11 (s, 1H, $H_{triazol}$), 4.61 (d, 1H, J=11.9 Hz, CH_2), 4.58 (d, 1H, J=11.9 Hz, CH_2). ^{13}C NMR (DMSO-d_6) *thymines*: 163.6 (C_{4A}, C_{4B}), 150.3 (C_{2A}, C_{2B}), 135.7 (C_{6A}), 135.5 (C_{6B}), 109.8 (C_{5A}, C_{5B}), 12.5 ($_{5A}CH_3$ or $_{5B}CH_3$), 12.4 ($_{5A}CH_3$ or $_{5B}CH_3$); *oses*: 84.1 ($C_{1'A}$ or $C_{1'B}$), 84.0 ($C_{1'A}$ or $C_{1'B}$), 83.8 ($C_{4'A}$), 81.9 ($C_{4'B}$), 79.1 ($C_{3'B}$), 70.8 ($C_{3'A}$), 52.0 ($C_{5'B}$), 51.3 ($C_{5'A}$), 38.0 ($C_{2'A}$), 35.4 ($C_{2'B}$); *linker*: 143.7 ($C_{triazol}$), 124.8 ($CH_{triazol}$), 62.1 (CH_2); mp=197–199 °C; IR (cm^{-1}): ν_{max}=3050, 2103, 1694; MS (IS) m/z=595.3 ($M+Na^+$).

4.4.3. Compound **6**

Isolation by preparative chromatography: $CHCl_3$/EtOH (7:3). ^1H NMR (DMSO-d_6) *thymines*: 11.33 (br s, 2H, 2NH), 11.30 (br s, 1H, NH), 7.41 (br s, 1H, H_{6B}), 7.39 (br s, 1H, H_{6C}), 7.34 (br s, 1H, H_{6A}), 1.79 (br s, 9H, $3CH_3$); *oses*: 6.17 (br t, 1H, J=7.0 Hz, $H_{1'A}$), 6.11 (br t, 1H, J=6.8 Hz, $H_{1'C}$), 6.09 (br t, 1H, J=6.5 Hz, $H_{1'B}$), 5.50 (d, 1H, J=4.3 Hz, OH), 4.72 (dd, 1H, J=4.4, 14.3 Hz, $H_{5'A}$ or $H_{5'B}$), 4.71 (dd, 1H, J=4.2, 14.1 Hz, $H_{5'A}$ or $H_{5'B}$), 4.64 (dd, 1H, J=7.1, 14.6 Hz, $H_{5'A}$ or $H_{5'B}$), 4.62 (dd, 1H, J=6.3, 14.1 Hz, $H_{5'A}$ or $H_{5'B}$), 4.35–4.25 (m, 3H, $H_{3'A}$, $H_{3'B}$, $H_{4'B}$), 4.26 (m, 1H, $H_{5'C}$), 4.20 (dd, 1H, J=5.5, 10.9 Hz, $H_{5'C}$), 4.17 (m, 1H, $H_{3'C}$), 4.11–4.06 (m, 2H, $H_{4'A}$, $H_{4'C}$), 2.35–2.05 (m, 6H, $H_{2'A}$, $H_{2'B}$, $H_{2'C}$); *linkers*: 8.11 (s, 1H, $H_{triazol}$), 8.09 (s, 1H, $H_{triazol}$), 4.59 (d, 1H, J=12.6 Hz, $_{A-B}CH_2$), 4.56 (d, 1H, J=12.6 Hz, $_{A-B}CH_2$), 4.55 (d, 1H, J=12.6 Hz, $_{B-C}CH_2$), 4.52 (d, 1H, J=12.6 Hz, $_{B-C}CH_2$); *tosyl*: 7.79 (d, 2H, J=8.2 Hz, H_2, H_6), 7.46 (d, 2H, J=8.2 Hz, H_3, H_5), 2.40 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) *thymines*: 163.6 (C_{4A}, C_{4B}, C_{4C}), 150.4 (2C: C_{2A} or C_{2B} or C_{2C}), 150.3 (1C: C_{2A} or C_{2B} or C_{2C}), 136.0 (2C: C_{6A} or C_{6B} or C_{6C}), 135.8 (1C: C_{6A} or C_{6B} or C_{6C}), 109.9 (1C: C_{5A} or C_{5B} or C_{5C}), 109.8 (2C: C_{5A} or C_{5B} or C_{5C}), 12.1 ($3CH_3$); *oses*: 84.4 ($C_{1'B}$ or $C_{1'C}$), 84.3 ($C_{1'B}$ or $C_{1'C}$), 84.0 ($C_{1'A}$), 83.9 ($C_{4'A}$), 81.5 ($C_{4'B}$), 80.8 ($C_{4'C}$), 79.0 ($C_{3'B}$), 78.3 ($C_{3'C}$), 70.7 ($C_{3'A}$), 70.1 ($C_{5'C}$), 51.3 ($C_{5'A}$ or $C_{5'B}$), 51.2 ($C_{5'A}$ or $C_{5'B}$), 37.9 ($C_{2'A}$), 35.6 ($C_{2'B}$), 35.1 ($C_{2'C}$); *linkers*: 143.7 ($C_{triazol}$), 143.6 ($C_{triazol}$), 124.7 ($CH_{triazol}$), 124.6 ($CH_{triazol}$), 62.1 ($2CH_2$); *tosyl*: 145.2 (C_4), 132.1 (C_1), 130.2 (C_3, C_5), 127.6 (C_2, C_6), 21.1 (CH_3); mp=170–173 °C; IR (cm^{-1}): ν_{max}=3055, 1686, 1364, 1176; MS (IS) m/z=1007.4 ($M+H^+$), 1029.3 ($M+Na^+$), 1045.3 (MK^+).

4.4.4. Compound **7**

Isolation by preparative chromatography: $CHCl_3$/EtOH (7:3). ^1H NMR (DMSO-d_6) *thymines*: 11.31 (s, 3H, 3NH), 7.52 (d, 1H, J=0.7 Hz, H_{6B}), 7.41 (d, 1H, J=0.6 Hz, H_{6C}), 7.35 (d, 1H, J=0.7 Hz, H_{6A}), 1.80 (br s, 3H, $_{5A}CH_3$ or $_{5B}CH_3$ or $_{5C}CH_3$), 1.79 (br s, 6H, $_{5A}CH_3$ or $_{5B}CH_3$ or $_{5C}CH_3$); *oses*: 6.16 (br t, 1H, J=7.0 Hz, $H_{1'A}$ or $H_{1'B}$), 6.14 (br t, 1H, J=6.7 Hz, $H_{1'A}$ or $H_{1'B}$), 6.11 (br t, 1H, J=6.7 Hz, $H_{1'C}$), 5.51 (d, 1H, J=4.4 Hz, OH), 4.73 (dd, 1H, J=4.2, 14.3 Hz, $H_{5'B}$), 4.70 (m, 2H, $H_{5'A}$, $H_{5'B}$), 4.62 (dd, 1H, J=7.6, 14.6 Hz, $H_{5'A}$), 4.32 (br ddd, J=2.6, 5.2 Hz, $H_{4'B}$), 4.30 (m, 1H, $H_{3'B}$), 4.29 (m, 1H, $H_{3'A}$), 4.17 (br ddd, 1H, J=2.7, 5.7 Hz, $H_{3'C}$), 4.09 (br dd, 1H, J=4.3, 7.7 Hz, $H_{4'A}$), 4.05 (br dd, 1H, J=4.1, 6.8 Hz, $H_{4'C}$), 3.59 (dd, 1H, J=6.2, 13.1 Hz, $H_{5'C}$), 3.55 (dd, 1H, J=5.2, 13.1 Hz, $H_{5'C}$), 2.35–2.23 (m, 4H, $H_{2'B}$, $H_{2'C}$), 2.19 (br dd, 1H, J=6.8, 13.7 Hz, $H_{2'A}$), 2.11 (ddd, 1H, J=3.9, 6.3, 13.4 Hz, $H_{2'A}$); *linkers*: 8.14 (s, 1H, $H_{triazol}$), 8.10 (s, 1H, $H_{triazol}$), 4.61 (d, 1H, J=12.2 Hz, $_{A-B}CH_2$), 4.58 (d, 1H, J=12.2 Hz, $_{A-B}CH_2$), 4.58 (d, 1H, J=12.2 Hz, $_{B-C}CH_2$), 4.55 (d, 1H, J=12.2 Hz, $_{B-C}CH_2$). ^{13}C NMR (DMSO-d_6) *thymines*: 163.6 (C_{4A}, C_{4B}, C_{4C}), 150.5 (1C: C_{2A} or C_{2B} or C_{2C}), 150.4 (2C: C_{2A} or C_{2B} or C_{2C}), 136.0 (C_{6A}, C_{6B}, C_{6C}), 109.9 (2C: C_{5A} or C_{5B} or C_{5C}), 109.8 (1C: C_{5A} or C_{5B} or C_{5C}), 12.1 ($3CH_3$); *oses*: 84.4 ($C_{1'C}$), 84.2 ($C_{1'B}$), 84.0 ($C_{1'A}$), 83.9 ($C_{4'A}$), 82.1 ($C_{4'C}$), 81.5 ($C_{4'B}$), 79.0 ($C_{3'B}$ or $C_{3'C}$), 78.9 ($C_{3'B}$ or $C_{3'C}$), 70.7 ($C_{3'A}$), 51.9 ($C_{5'C}$), 51.3 ($C_{5'A}$ or $C_{5'B}$), 51.2 ($C_{5'A}$ or $C_{5'B}$), 37.9 ($C_{2'A}$), 35.2 ($C_{2'B}$ or $C_{2'C}$), 35.0 ($C_{2'B}$ or $C_{2'C}$); *linkers*: 143.8 ($C_{triazol}$), 143.6 ($C_{triazol}$), 124.7 ($2CH_{triazol}$), 62.1 (CH_2), 62.0 (CH_2); mp=240–242 °C; IR (cm^{-1}): ν_{max}=3360, 2103, 1686; MS (IS) m/z=900.3 ($M+Na^+$).

4.4.5. Compound **8**

Isolation by precipitation. ^1H NMR (DMSO-d_6) *thymines*: 11.34 (br s, 3H, 3NH), 11.31 (br s, 1H, NH), 7.41 (br s, 1H, H_{6B}), 7.40 (br s, 1H, H_{6C} or H_{6D}), 7.39 (br s, 1H, H_{6C} or H_{6D}), 7.35 (br s, 1H, H_{6A}), 1.79 (br s, 9H, $_{5A}CH_3$, $_{5C}CH_3$, $_{5D}CH_3$), 1.77 (br s, 3H, $_{5B}CH_3$); *oses*: 6.17 (br t, 1H, J=7.0 Hz, $H_{1'A}$), 6.12 (br t, 1H, J=6.0 Hz, $H_{1'B}$ or $H_{1'C}$ or $H_{1'D}$), 6.11 (br t, 1H, J=7.1 Hz, $H_{1'B}$ or $H_{1'C}$ or $H_{1'D}$), 6.09 (br t, 1H, J=6.5 Hz, $H_{1'B}$ or $H_{1'C}$ or $H_{1'D}$), 5.52 (d, 1H, J=4.3 Hz, OH), 4.73 (dd, 1H, J=4.6, 14.5 Hz, $H_{5'B}$ or $H_{5'C}$), 4.72 (dd, 1H, J=4.2, 14.0 Hz, $H_{5'A}$), 4.70 (m, 2H, $H_{5'B}$ or $H_{5'C}$), 4.65 (dd, 1H, J=7.4, 14.4 Hz, 1H, $H_{5'B}$ or $H_{5'C}$), 4.62 (dd, 1H, J=6.6, 14.0 Hz, $H_{5'A}$), 4.35–4.25 (m, 5H, $H_{3'A}$, $H_{3'B}$, $H_{4'B}$, $H_{3'C}$, $H_{4'C}$), 4.26 (m, 1H, $H_{5'D}$), 4.21 (dd, 1H, J=5.5, 10.9 Hz, $H_{5'D}$), 4.17 (m, 1H, $H_{3'D}$), 4.11–4.06 (m, 2H, $H_{4'A}$, $H_{4'D}$), 2.35–2.15 (m, 8H, $H_{2'A}$, $H_{2'B}$, $H_{2'C}$, $H_{2'D}$); *linkers*: 8.12 (s, 1H, $H_{triazol}$), 8.11 (s, 1H, $H_{triazol}$), 8.10 (s, 1H, $H_{triazol}$), 4.57 (m, 4H, $_{A-B}CH_2$, $_{B-C}CH_2$), 4.54 (d, 1H, J=12.6 Hz, $_{C-D}CH_2$), 4.51 (d, 1H, J=12.6 Hz, $_{C-D}CH_2$); *tosyl*: 7.79 (d, 2H, J=8.2 Hz, H_2, H_6), 7.46 (d, 2H, J=8.2 Hz, H_3, H_5), 2.39 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) *thymines*: 163.6 (1C: C_{4A} or C_{4B} or C_{4C} or C_{4D}), 163.5 (3C: C_{4A} or C_{4B} or C_{4C} or C_{4D}), 150.3 (C_{2A}, C_{2B}, C_{2C}, C_{2D}), 135.9 (C_{6A}, C_{6C}, C_{6D}), 135.7 (C_{6B}), 109.8 (C_{5A}, C_{5B}, C_{5C}, C_{5D}), 12.0 ($4CH_3$); *oses*: 84.3 (2C: $C_{1'B}$ or $C_{1'C}$ or $C_{1'D}$), 84.2 (1C: $C_{1'B}$ or $C_{1'C}$ or $C_{1'D}$), 83.9 ($C_{1'A}$), 83.8 ($C_{4'A}$), 81.4 ($C_{4'B}$, $C_{4'C}$), 80.8 ($C_{4'D}$), 78.9 ($C_{3'B}$, $C_{3'C}$), 78.2 ($C_{3'D}$), 70.6 ($C_{3'A}$), 70.0 ($C_{5'D}$), 51.2 (2C: $C_{5'A}$ or $C_{5'B}$ or $C_{5'C}$), 51.1 (1C: $C_{5'A}$ or $C_{5'B}$ or $C_{5'C}$), 37.8 ($C_{2'A}$), 35.5 ($C_{2'B}$), 35.0 ($C_{2'C}$, $C_{2'D}$); *linkers*: 143.6 (2C: $C_{triazol}$), 143.5 ($C_{triazol}$), 124.7 ($CH_{triazol}$), 124.6 (2C: $CH_{triazol}$), 62.0 ($3CH_2$); *tosyl*: 145.1 (C_4), 131.9 (C_1), 130.1 (C_3, C_5), 127.5 (C_2, C_6), 20.7 (CH_3); mp=197–199 °C; IR (cm^{-1}): ν_{max}=3056, 1698, 1369; MS (IS) m/z=1334 ($M+Na^+$).

4.4.6. Compound **9**

Isolation by work-up (THF/$CHCl_3$/H_2O). ^1H NMR (DMSO-d_6) *thymines*: 11.32 (br s, 4H, 4NH), 7.52 (br s, 1H, H_{6B}), 7.40 (br s, 2H, H_{6C}, H_{6D}), 7.35 (br s, 1H, H_{6A}), 1.80 (br s, 6H, $_{5C}CH_3$, $_{5D}CH_3$), 1.79 (br s, 6H, $_{5A}CH_3$, $_{5B}CH_3$); *oses*: 6.17 (br t, 1H, J=7.0 Hz, $H_{1'A}$), 6.15 (br t, 1H, J=7.9 Hz, $H_{1'B}$ or $H_{1'C}$ or $H_{1'D}$), 6.12 (br t, 1H, J=7.2 Hz, $H_{1'B}$ or $H_{1'C}$ or $H_{1'D}$), 6.11 (br t, 1H, J=7.0 Hz, $H_{1'B}$ or $H_{1'C}$ or $H_{1'D}$), 5.52 (br s, 1H, OH), 4.75–4.65 (m, 5H, $H_{5'A}$ or $H_{5'B}$ or $H_{5'C}$), 4.62 (dd, 1H, J=7.6, 14.6 Hz, $H_{5'A}$), 4.35–4.26 (m, 5H, $H_{3'A}$, $H_{3'B}$, $H_{4'B}$, $H_{3'C}$, $H_{4'C}$), 4.17 (br dd, 1H, J=2.8, 5.6 Hz, $H_{3'D}$), 4.09 (br dd, 1H, J=4.2, 7.6 Hz, $H_{4'A}$), 4.05 (br dd, 1H, J=3.0, 6.3 Hz, $H_{4'D}$), 3.59 (dd, 1H, J=6.3, 13.0 Hz, $H_{5'D}$), 3.55 (dd, 1H, J=4.6, 13.1 Hz, $H_{5'D}$), 2.34–2.22 (m, 6H, $H_{2'B}$, $H_{2'C}$, $H_{2'D}$), 2.19 (br dd, 1H, J=7.1, 13.3 Hz, $H_{2'A}$), 2.11 (ddd, 1H, J=4.0, 6.3, 13.4 Hz, $H_{2'A}$); *linkers*: 8.14 (s, 1H, $H_{triazol}$), 8.12 (s, 1H, $H_{triazol}$), 8.10 (s, 1H, $H_{triazol}$), 4.60 (d, 2H, J=12.2 Hz, $_{A-B}CH_2$ or $_{B-C}CH_2$ or $_{C-B}CH_2$), 4.58 (d, 4H, J=12.2 Hz, $_{A-B}CH_2$ or $_{B-C}CH_2$ or $_{C-B}CH_2$). ^{13}C NMR (DMSO-d_6) *thymines*: 163.6 (C_{4A}, C_{4B}, C_{4C}, C_{4D}), 150.5 (1C: C_{2A} or C_{2B} or C_{2C} or C_{2D}), 150.4 (3C: C_{2A} or C_{2B} or C_{2C} or C_{2D}), 136.1 (C_{6A}, C_{6B}, C_{6C}, C_{6D}), 109.9 (C_{5A}, C_{5B}, C_{5C}, C_{5D}), 12.1 ($4CH_3$); *oses*: 84.5 (2C: $C_{1'B}$ or $C_{1'C}$ or $C_{1'D}$), 84.2 (1C: $C_{1'B}$ or $C_{1'C}$ or $C_{1'D}$), 84.0 ($C_{1'A}$), 83.9 ($C_{4'A}$), 82.1 ($C_{4'D}$), 81.6 ($C_{4'B}$, $C_{4'C}$), 79.0 ($C_{3'B}$, $C_{3'C}$), 78.9 ($C_{3'D}$), 70.7 ($C_{3'A}$), 51.9 ($C_{5'D}$), 51.2 (2C: $C_{5'A}$ or $C_{5'B}$ or $C_{5'C}$), 51.1 (1C: $C_{5'A}$ or $C_{5'B}$ or $C_{5'C}$), 37.9 ($C_{2'A}$), 35.2 (1C: $C_{2'B}$ or $C_{2'C}$ or $C_{2'D}$), 35.1 (2C: $C_{2'B}$ or $C_{2'C}$ or $C_{2'D}$); *linkers*: 143.8 ($C_{triazol}$), 143.7 ($C_{triazol}$), 143.6 ($C_{triazol}$), 124.8 ($CH_{triazol}$), 124.7 (2C: $CH_{triazol}$), 62.1 (2C: CH_2), 62.0 (CH_2); mp=140 °C; IR (cm^{-1}): ν_{max}=2103; MS (IS) m/z=1205.4 ($M+Na^+$).

4.4.7. Compound **10**

Isolation by precipitation using H_2O. ^1H NMR (DMSO-d_6) *thymines*: 11.33 (br s, 5H, 5NH), 7.47 (br s, 1H, H_{6A} or H_{6B} or H_{6C} or H_{6D} or H_{6E}), 7.38 (br s, 3H, H_{6A} or H_{6B} or H_{6C} or H_{6D} or H_{6E}), 7.33 (br s, 1H, H_{6A} or H_{6B} or H_{6C} or H_{6D} or H_{6E}), 1.79 (br s, 15H, $_{5A}CH_3$, $_{5B}CH_3$, $_{5C}CH_3$, $_{5D}CH_3$, $_{5E}CH_3$); *oses*: 6.16 (br t, 2H, J=7.0 Hz, $H_{1'A}$ or $H_{1'B}$ or $H_{1'C}$ or

$H_{1'D}$ or $H_{1'E}$), 6.10 (br t, 3H, J=6.9 Hz, $H_{1'A}$ or $H_{1'B}$ or $H_{1'C}$ or $H_{1'D}$ or $H_{1'E}$), 5.56 (br d, 1H, J=2.0 Hz, OH), 4.74–4.58 (m, 8H, $H_{5'A}$, $H_{5'B}$, $H_{5'C}$, $H_{5'D}$), 4.38–4.20 (m, 9H, $H_{3'A}$, $H_{3'B}$, $H_{4'B}$, $H_{3'C}$, $H_{4'C}$, $H_{3'D}$, $H_{4'D}$, $H_{5'E}$), 4.17 (m, 1H, $H_{3'E}$), 4.10–4.07 (m, 2H, $H_{4'A}$, $H_{4'E}$), 2.30–2.09 (m, 10H, $H_{2'A}$, $H_{2'B}$, $H_{2'C}$, $H_{2'D}$, $H_{2'E}$); *linkers*: 8.12 (br s, 3H, $H_{triazol}$), 8.09 (s, 1H, $H_{triazol}$), 4.58 (m, 8H, $_{A-B}CH_2$, $_{B-C}CH_2$, $_{C-D}CH_2$, $_{D-E}CH_2$); *tosyl*: 7.78 (d, 2H, J=8.0 Hz, H_2, H_6), 7.48 (d, 2H, J=8.0 Hz, H_3, H_5), 2.39 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6) *thymines*: 163.7 (C_{4A}, C_{4B}, C_{4C}, C_{4D}, C_{4E}), 150.4 (C_{2A}, C_{2B}, C_{2C}, C_{2D}, C_{2E}), 136.1 (C_{6A}, C_{6B}, C_{6C}, C_{6D}, C_{6E}), 109.9 (C_{5A}, C_{5B}, C_{5C}, C_{5D}, C_{5E}), 12.1 (5CH_3); *oses*: 84.5 (2C: $C_{1'B}$ or $C_{1'C}$ or $C_{1'D}$), 84.4 (1C: $C_{1'B}$ or $C_{1'C}$ or $C_{1'D}$), 84.1 ($C_{1'A}$, $C_{1'E}$), 83.9 ($C_{4'A}$), 81.5 ($C_{4'B}$, $C_{4'C}$, $C_{4'D}$, $C_{4'E}$), 79.1 (1C: $C_{3'B}$ or $C_{3'C}$ or $C_{3'D}$ or $C_{3'E}$), 79.0 (3C: $C_{3'B}$ or $C_{3'C}$ or $C_{3'D}$ or $C_{3'E}$), 70.7 ($C_{3'A}$), 67.0 ($C_{5'E}$), 51.3 (3C: $C_{5'A}$ or $C_{5'B}$ or $C_{5'C}$ or $C_{5'D}$), 51.2 (1C: $C_{5'A}$ or $C_{5'B}$ or $C_{5'C}$ or $C_{5'D}$), 37.9 ($C_{2'A}$), 35.1 ($C_{2'B}$, $C_{2'C}$, $C_{2'D}$, $C_{2'E}$); *linkers*: 143.7 (2C: $C_{triazol}$), 143.6 (2C: $C_{triazol}$), 124.8 ($CH_{triazol}$), 124.7 (3C: $CH_{triazol}$), 62.1 (3CH_2), 61.7 (1CH_2); *tosyl*: 145.2 (C_4), 132.2 (C_1), 130.2 (C_3, C_5), 127.6 (C_2, C_6), 20.8 (CH_3); mp=277 °C; IR (cm^{-1}): ν_{max}=3055, 1690, 1366; MS (IS) m/z=1639 ($M+Na^+$).

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Supplementary data

Supplementary data (spectroscopic data) associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.006.

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