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PYRIMIDINE-PURINE AND PYRIMIDINE HETERODINUCLEOSIDES SYNTHESIS CONTAINING A TRIAZOLE LINKAGE

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□ *This article describes a synthetic route to generate two purine-pyrimidine and pyrimidine heterod-inucleosides. Both microwave activated regioselective alkylation using hydride and copper-catalyzed-azide-alkyne-cycloaddition (CuAAC) were used in order to perform the synthesis.*

Keywords Oligonucleotides analogues; click chemistry; microwave-activated synthesis

INTRODUCTION

Synthetic oligonucleotide analogues are of considerable importance because of their ability to inhibit gene expression through the antisense effect.^[1] One of the most important modifications is the complete substitution of the phosphate internucleoside bridge,^[2] in order to achieve stronger affinity for the nucleic acid target, enhanced resistance, and improved membrane permeability and cellular uptake. The Huisgen 1,3-dipolar cycloaddition between azides and alkynes, performed by recently discovered copper (I) catalysis^[3] appears as a promising way to generate oligomers and particularly oligonucleotide analogues, which can resist chemical or enzymatic depolymerization. Moreover the exclusive regioselective formation of 1,4-disubstituted-1,2,3-triazole conserves the directional character of DNA strands. In addition the introduction of a **dT-A** or pyrimidine-purine step into a straight and rigid A-tract of oligonucleoside can cause a positive roll deformation that kinks the DNA helix at this step.^[4] In this way, our research effort in this area has focused on the synthesis of an anti HIV-1 sequence (Figure 1)^[5] and the introduction of a **dT-A** step in this sequence. Previous studies, introducing a triazole linkage in oligonucleosides backbone, have been realized using thymidine as nucleoside (homothymidines) in both

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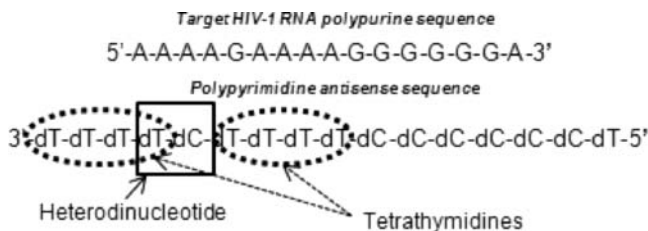


FIGURE 1 Anti HIV-1 sequence.

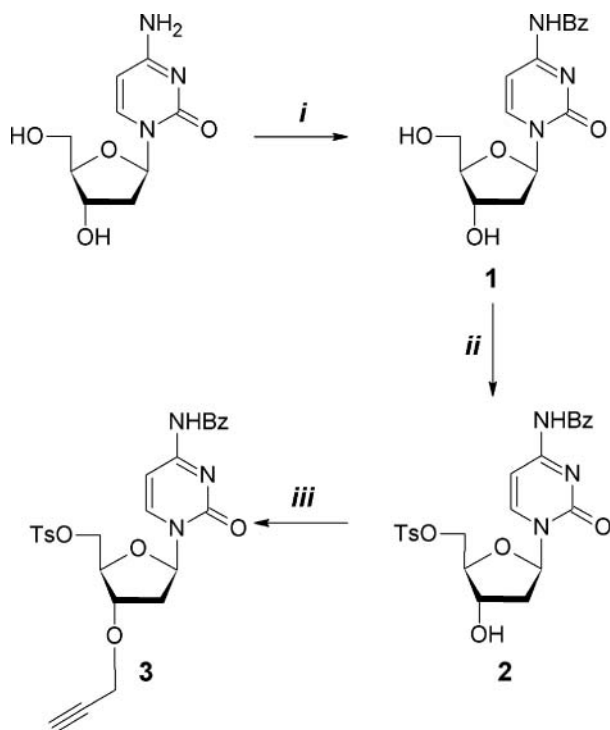
solution-phase and solid phase synthesis.^[6] However, no other pyrimidine or purine nucleosides have been inserted in a oligonucleotide sequences using a “click backbone.”

In this article, we are interested in the feasibility of coupling two different nucleosides by click chemistry and synthesis of two hetero-dinucleoside analogues (**dC-dT** and **dT-A**) in which glycosidic moieties are linked by a triazole group between positions 3' and 5'.

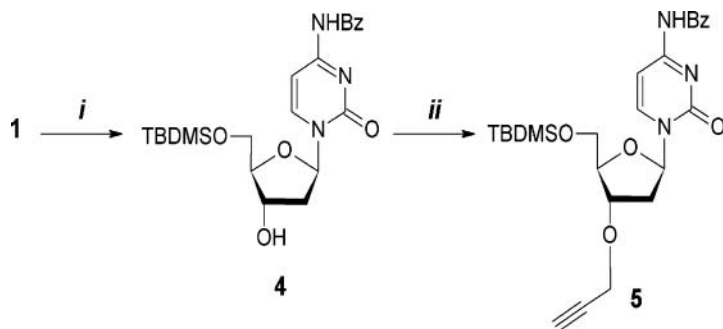
RESULTS AND DISCUSSION

Toward a Cytidine-Thymidine heterodimer (dC-dT)

The synthesis of the first precursor **3** began benzoylating commercially available 2'-deoxycytidine, using an established transient protection method,^[7] in order to protect the exo-cyclic amine on the nucleobase to give compound **1** (87%). Then tosylation^[8] of resultant *N*⁴-benzoyl-2'-deoxycytidine **1** using tosyl chloride (1.6 equiv.) and standard conditions in pyridine, at 0°C produced compound **2** in low yield (49%; Scheme 1). In addition to 5'-*O*-tosyldeoxycytidine, 3',5'-di-*O*-tosyldeoxycytidine also is observed. This result strongly suggests that the slight difference in reactivity between 5' and 3' positions is the cause of relative low yield of tosylation of primary hydroxyl group. Alkyne **3** was obtained by regioselective 3'-*O*-alkylation using a two-step method.^[9] During the first step compound **2** was activated with 2.5 equivalents of NaH in THF, then, for the second step, 2.5 equivalents of propargyl bromide was added and the mixture was activated again. No evolution of hydrogen gas was observed and a large amount of reactant (5 equiv.) was necessary in order to obtain the compound **3** in 51% yield. This strategy is not efficient to prepare compound **3** because the overall yield is very low (22% from deoxycytidine). Finally, for obtention of the alkyne compound, we decided to use another strategy (Scheme 2). Precursor **5** was synthesized from *N*⁴-benzoyl-2'-deoxycytidine **1**, first by selective protection of 5'-hydroxyl group with *tert*-butyldimethylsilyl chloride (1.6 equiv.) in dry dimethylformamide (DMF) in the presence of imidazole (3.0 equiv.) giving compound **4** in 84% yield.^[10] The 3'-hydroxyl group was

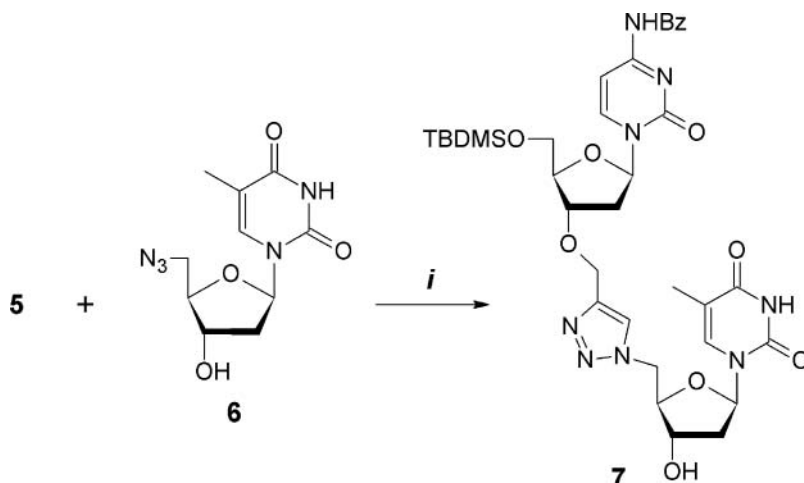


SCHEME 1 Synthesis of propargylated 2'-deoxycytidin precursor (**3**). Reagents and conditions: (i) 1-Me₃SiCl (5 equiv.), 2-BzCl (5 equiv.), Py (10 mL); (ii) TsCl (1.6 equiv.), Py, 0°C; (iii) 1-NaH (2.5 equiv.), THF, MW (2 minutes, 200 W, 40°C) 2-propargylbromide (2.5 equiv.); (6 minutes, 200 W, 40°C).



SCHEME 2 Synthesis of the second propargylated 2'-deoxycytidine precursor (**5**). Reagents and conditions: (i) Imidazole (3 equiv.), TBDMSCl (1.6 equiv.), DMF; (ii) 1-NaH (2.5 equiv.), THF, MW (2 minutes, 200 W, 40°C) 2-propargylbromide (2.5 equiv.), MW (6 minutes, 200 W, 40°C).

then alkylated using Chattopadhyaya's method^[9] with NaH (2.5 equiv.) and propargylbromide (2.5 equiv.) in THF under MW activation to give alkyne compound **5** in 91% yield (67% from deoxycytidine). The azido-precursor was 5'-azido-5'-deoxythymidine.^[6] Tosylation of thymidine followed by an azidation gave the expected precursor **6** in a two steps good yield of 67% from thymidine.

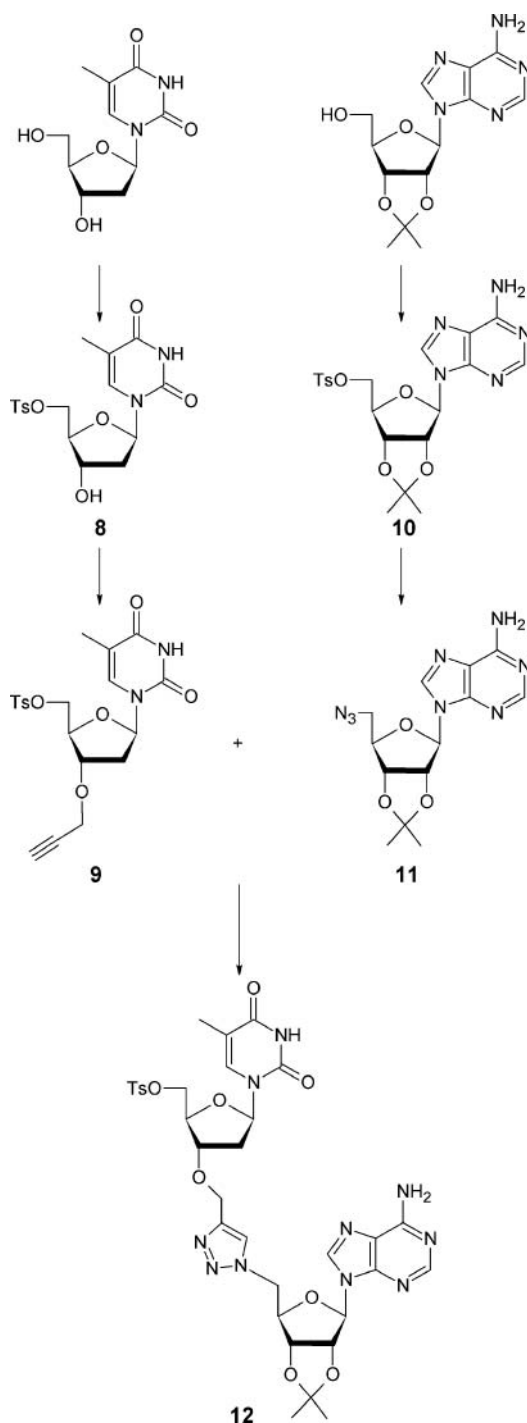


SCHEME 3 Synthesis of the **dC-dT** heterodinucleotide analogue (**7**). Reagents and conditions: (i) CuSO_4 (0.1 equiv.), Na ascorbate (0.6 equiv.), $\text{H}_2\text{O}/\text{EtOH}$ (1/1), MW (1 minutes, 200 W, 80°C).

Derivatives **5** and **6** were then coupled using copper(I)-catalyzed cycloaddition in order to obtain silylated heterodimer **7** (Scheme 3). Optimization of this reaction has been described in a previous article.^[11] Alkyne and azide precursors were suspended in a 1:1 mixture of water and ethanol, together with Cu(I) catalyst and sodium ascorbate. After 3 minutes of MW irradiation the heterodimer **7** was isolated in 70% yield.

Synthesis of an Thymidine-Adenosine heterodimer (dT-A)

The synthesis of hetero-dinucleoside analogue **dT-A** is presented in Scheme 4. The first precursor synthesized was 3'-O-propargyl-5'-O-tosylthymidine. Selective tosylation of the primary hydroxyl group of thymidine gave the already known product **8**. Alkyne **9** was obtained by regioselective 3'-O-alkylation using Chattopadhyaya's two-step method under microwave irradiation. During the first step compound **8** was activated (40°C , 200 W, 3 minutes) with 2.5 equivalents of NaH in THF then in the second step 2.5 equivalents of propargyl bromide was added and the mixture was subjected to microwave irradiation for 3 minutes. The reaction produced compound **9** in 96% yield.^[6] The synthesis of second precursor **11** began with tosylating commercially available 2',3'-O-isopropylidene adenosine. Then using previous method used for hydroxyl group protection, the protected compound **10** was synthesized in moderate yield (50%). In addition to 5'-O-tosyl-2',3'-O-isopropylidene adenosine, cycloadenosine **10'** was also observed (Figure 2). Compound **10'** results from the intramolecular nucleophilic displacement by N^3 (Figure 2). It was reported that, upon rotation of the adenine ring of 5'-protected adenosine, the N^3 of the base can



SCHEME 4 Synthesis of the dT-A heterodinucleotide analogue (**12**).

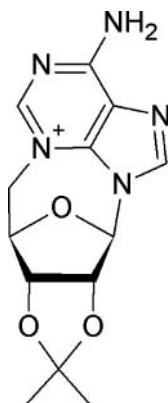


FIGURE 2 Cycloadenosine 10'.

readily displace the 5'-activation to give the ionic cycloadenosine, causing a steep decrease of the overall yield of **10**.^[12] In fact, intramolecular displacement of sulfonate is so rapid that it interferes with product isolation and purification.

Derivatives **9** and **11** were then clicked using copper(I)-catalyzed cycloaddition in order to obtain silylated heterodimer **12**. Alkyne and azide precursors were suspended in a 1:1 mixture of water and ethanol, together with Cu(I) catalyst and sodium ascorbate. After 3 minutes of irradiation, heterodimer **12** was obtained after purification in 87% yield. The tosyl group in 5' of the **dT-A** could be used for further azidation in order to generate an oligonucleotides analogue.

CONCLUSION

In conclusion we have investigated the first total synthesis of two triazole heterodimers (**dC-dT** and **dT-A**) using a “click chemistry” reaction and MW irradiation to reduce reaction time. This work is presently continuing toward solid-phase synthesis of a pyrimidine antisense sequence with promising results.

EXPERIMENTAL

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 F₂₅₄ (Merck) plates and visualized in several ways: with an ultraviolet light source at 254 nm, by spraying with sulphuric acid (6N) 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 (Germany). Chemical shifts (δ) are expressed in ppm with Me₄Si as an internal standard ($\delta = 0$). 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.

Tosylation of *N*⁴-Benzoyl-2'-deoxycytidine

*N*⁴-benzoyl-2'-deoxycytidine **1** (223 mg, 0.68 mmol) was solubilized in anhydrous pyridine with 1.6 equivalents of tosyl chloride (206 mg, 1.08 mmol). This solution was placed under argon at 0°C during 3 hours. Then solvent was removed under reduced pressure and the crude residue purified using flash chromatography (CH₂Cl₂/petroleum ether, from 8/2 to pure petroleum ether). Pure product **2** was recovered as a white solid in 49% yield (160 mg).

Silylation of *N*⁴-Benzoyl-2'-deoxycytidine

*N*⁴-benzoyl-2'-deoxycytidine **1** (150 mg, 0.45 mmol) was solubilized in anhydrous DMF with 3.0 equivalents of imidazole (92.5 mg, 1.36 mmol) and 1.6 equivalents of *tert*-butyldimethylsilyl chloride (109 mg, 0.73 mmol). This solution was placed under argon at 0°C during 3 hours. Then solvent was removed under reduced pressure and the crude residue purified using flash chromatography. Pure product **4** was recovered as a white solid in 84% yield (184 mg).

General Procedure for Propargylation

To compound **4** (50 mg, 0.10 mmol) in dry THF (15 mL), were added 2.5 equivalents of NaH (60%, 10 mg, 0.26 mmol) and the mixture was activated by microwave irradiation (2 minutes, 200 W, 40°C). Two and half equivalents of propargyl bromide (30 μ L, 0.26 mmol) were then added and the mixture was activated by microwave irradiation (6 minutes, 200W, 40°C). After work-up (NH₄Cl/H₂O), the product was purified by chromatography (thick layer plates, AcOEt/MeOH (9/1)). Compound **5** was recovered in 91% yield (39 mg).

General Procedure for Click Reaction

Compounds **9** (217 mg, 0.50 mmol), **11** (167 mg, 0.50 mmol), sodium ascorbate (300 μ L, 1 M, 0.6 equiv.), and copper sulfate pentahydrate (7.5 mg, 0.1 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 1 minutes at 80°C, using an irradiation power of 200 W. After work-up (THF), the crude residue was concentrated in vacuo and product **12** was recovered as a white solid in 85% yield (326.2 mg).

CHARACTERIZATIONS

Spectroscopic data of selected new compounds:

Compound 4: $R_f = 0.52$ (AcOEt/EtOH: 9/1); ^1H NMR (DMSO d_6): *cytidine*: 11.22 (s, 1H, NH), 8.31 (br s, 1H, H_5), 7.36 (br d, $J = 6.8$ Hz, H_5); *benzoyl*: 8.00 (dd, 2H, $J = 1.2$ Hz, $J = 8.5$ Hz, H_{2-6}), 7.62 (br t, 1H, $J = 7.5$ Hz, H_4), 7.51 (br t, 2H, $J = 7.5$ Hz, H_{3-5}); *ose*: 6.13 (t, 1H, $J = 6.1$ Hz, $\text{H}_{1'}$), 5.33 (d, 1H, $J = 4.4$ Hz, 1H, $\text{O}_3'\text{-H}$), 4.22 (m, 1H, $\text{H}_{3'}$), 3.93 (br dd, 1H, $J = 3.1$ Hz, $J = 11.5$ Hz, $\text{H}_{5'a}$), 3.87 (dd, 1H, $J = 3.3$ Hz, $J = 11.5$ Hz, $\text{H}_{5'b}$), 2.36 (ddd, 1H, $J = 4.8$ Hz, $J = 6.1$ Hz, $J = 13.3$ Hz, $\text{H}_{2'a}$), 2.07 (dt, 1H, $J = 6.1$ Hz, $J = 13.3$ Hz, $\text{H}_{2'b}$); *TBDMS*: 0.88 (s, 9H, C- CH_3), 0.09 (s, 6H, Si- CH_3); ^{13}C NMR (DMSO d_6): *thymine*: 162.9 (C4), 154.3 (C2), 144.4 (C6), 95.8 (C5); *benzoyl*: 167.3 (C=O), 133.1 (C1), 132.7 (C4), 128.4 (C2, C3, C5, C6); *ose*: 87.3 (C4'), 86.2 (C1'), 69.6 (C3'), 62.6 (C5'), 41.2 (C2'); *TBDMS*: 25.7 (C- CH_3), 17.9 (C- CH_{3a}), -5.5 (Si- CH_{3a}), -5.6 (Si- CH_{3b}).

Compound 5: $R_f = 0.45$ (AcOEt/MeOH: 9/1); ^1H NMR (DMSO d_6): *cytidine*: 11.26 (s, 1H, NH), 8.28 (br s, 1H, H_5), 7.36 (br d, $J = 7.4$ Hz, H_5); *benzoyl*: 8.01 (dd, 2H, $J = 7.2$ Hz, $J = 1.2$ Hz, H_{2-6}), 7.62 (br t, 1H, $J = 7.4$ Hz, H_4), 7.51 (br t, 2H, $J = 7.6$ Hz, H_{3-5}); *ose*: 6.09 (br t, 1H, $J = 6.4$ Hz, $\text{H}_{1'}$), 4.27 (m, 1H, $\text{H}_{3'}$), 4.14 (br dd, 1H, $J = 3.1$ Hz, $J = 6.2$ Hz, $\text{H}_{4'}$), 3.87 (br dd, 1H, $J = 3.7$ Hz, $J = 11.4$ Hz, $\text{H}_{5'a}$), 3.78 (br dt, 1H, $J = 3.3$ Hz, $J = 11.4$ Hz, $\text{H}_{5'b}$), 2.54 (ddd, 1H, $J = 3.1$ Hz, $J = 6.1$ Hz, $J = 13.3$ Hz, $\text{H}_{2'a}$), 2.14 (dt, 1H, $J = 6.3$ Hz, $J = 13.3$ Hz, $\text{H}_{2'b}$); *TBDMS*: 0.89 (s, 9H, C- CH_3), 0.10 (s, 6H, Si- CH_{3a}), 0.09 (s, 6H, Si- CH_{3b}); *propargyl*: 4.23 (br d, 1H, $J = 2.3$ Hz, $J = 18.0$ Hz, CH_2), 3.47 (t, 1H, $J = 2.3$ Hz, C-H); ^{13}C NMR (DMSO d_6): *thymine*: 163.0 (C4), 154.2 (C2), 144.3 (C6), 95.9 (C5); *benzoyl*: 167.3 (C=O), 133.1 (C1), 132.7 (C4), 128.4 (C2, C3, C5, C6); *ose*: 86.5 (C1'), 84.5 (C4'), 77.7 (C3'), 62.8 (C5'), 40.4 (C2'); *TBDMS*: 25.7 (C- CH_3), 17.9 (C- CH_3), -5.6 (CH $_{3a}$), -5.6 (CH $_{3b}$); *propargyl*: 80.0 (C), 77.4 (CH), 55.9 (CH $_2$); MS (IS) $m/z = 484.4$ (MH $^+$), 506.4 (MNa $^+$), 989.7 (M $_2$ Na $^+$).

Compound 7: $R_f = 0.20$ (CHCl $_3$ /EtOH: 9/1); ^1H NMR (DMSO d_6): 11.29 (s, 2H, NH), 2.52–2.06 (m, 4H, $\text{H}_{2'}$ cytidine and thymine); *cytidine*: 8.28 (d, 1H, $J = 7.4$ Hz, H_5), 7.34 (d, 1H, $J = 7.4$ Hz, H_6); *ose*: 6.10 (t, 1H, $J = 6.4$ Hz, $\text{H}_{1'}$), 4.29 (m, 1H, $\text{H}_{3'}$), 4.14 (m, 1H, $\text{H}_{4'}$), 3.85 (dd, 1H, $J = 3.5$ Hz, $J = 11.5$ Hz, $\text{H}_{5'}$), 3.75 (dd, 1H, $J = 3.2$ Hz, $J = 11.5$ Hz, $\text{H}_{5'}$); *TBDMS*: 0.86 (s, 9H, C-(CH $_3$) $_3$), 0.07 (s, 3H, Si- CH_{3a}), 0.06 (s, 3H, Si- CH_{3b}); *benzoyl*: 8.01 (dd, 2H, $J = 1.2$ Hz, $J = 7.4$ Hz), 7.62 (br. t, 1H, $J = 7.4$ Hz), 7.51 (br. t, 2H, $J = 7.7$ Hz); *linker*: 8.09 (s, 1H, $\text{H}_{\text{triazole}}$), 4.57 (d, 2H, $J = 12.1$ Hz, CH $_{2\text{triazole}}$); *thymine*: 7.35 (s, 1H, H_6), 1.80 (s, 3H, CH $_3$); *ose*: 6.15 (t, 1H, $J = 6.9$ Hz, $\text{H}_{1'}$), 5.50 (br. s, 1H, OH), 4.71 (dd, 1H, $J = 4.3$ Hz, $J = 14.4$ Hz, $\text{H}_{5'}$), 4.70 (dd, 1H, $J = 3.4$ Hz, $J = 14.4$ Hz, $\text{H}_{5'}$), 4.20 (m, 1H, $\text{H}_{3'}$), 4.08 (m, 1H, $\text{H}_{4'}$); ^{13}C NMR (DMSO d_6): 41.4 (C2' cytidine or thymidine), 37.5 (C2' cytidine or thymidine); *cytidine*: 163.0 (C4), 154.2 (C2), 144.3 (C6), 95.9 (C5); *ose*: 86.5 (C1'), 84.9 (C4'), 78.1 (C3'); *benzoyl*: 167.2 (C=O), 133.1 (C1), 132.7 (C4), 128.4 (C2, C3, C5, C6); *TBDMS*: 25.7 (C- CH_3), 17.9 (C- CH_3);

linker: 143.7 (C_{triazole}), 124.7 (CH_{triazole}), 61.8 (CH_{2triazole}), -5.6 (CH_{3a}), -5.7 (CH_{3b}); *thymine*: 163.6 (C4), 150.4 (C2), 136.0 (C6), 109.8 (C5), 12.1 (CH₃); *ose*: 84.0 (C1'), 83.9 (C4'), 79.1 (C3').

Compound 10: R_f = 0.21 (CHCl₃/EtOH: 9/1); ¹H NMR (DMSO *d*₆): *adenine*: 8.21 (s, 1H, H₈), 8.03 (s, 1H, H₂), 7.36 (br s, NH₂); *ose*: 6.18 (d, 1H, J = 1.8 Hz, H_{1'}), 5.33 (dd, 1H, J = 1.8 Hz, J = 6.2 Hz, H_{2'}), 5.00 (m, 1H, H_{3'}), 4.33 (m, 1H, H_{4'}), 4.33 (dd, 1H, J = J = 3.9 Hz, 12.2 Hz, H_{5'a}), 4.22 (dd, 1H, J = 2.8 Hz, J = 7.0 Hz, H_{5'b}); *isopropylidene*: 1.51 (s, 3H, CH_{3a}), 1.29 (s, 1H, CH_{3b}); *tosyl*: 7.56 (d, 2H, J = 8.2 Hz, H_{ortho/S}), 7.25 (d, 2H, J = 8.2 Hz, H_{meta/S}), 2.36 (s, 3H, CH₃).

Compound 11: R_f = 0.50 (CH₂Cl₂/EtOH: 9/1); ¹H NMR (DMSO *d*₆): *adenine*: 8.35 (s, 1H, H₈), 8.18 (s, 1H, H₂), 7.35 (s, NH₂); *ose*: 6.22 (d, 1H, J = 2.6 Hz, H_{1'}), 5.52 (dd, 1H, J = 2.6 Hz, J = 6.2 Hz, H_{2'}), 5.01 (dd, 1H, J = 3.0 Hz, J = 6.2 Hz, H_{3'}), 4.31 (m, 1H, H_{4'}), 3.63 (dd, 1H, J = 7.2 Hz, 13.0 Hz, H_{5'a}), 3.55 (dd, 1H, J = 4.9 Hz, J = 13.0 Hz, H_{5'b}); *isopropylidene*: 1.55 (s, 3H, CH_{3a}), 1.13 (s, 1H, CH_{3b}); ¹³C NMR (DMSO *d*₆): *adenine*: 156.2 (C6), 152.8 (C2), 148.8 (C4), 140.0 (C8), 119.2 (C5); *ose*: 84.3 (C1'), 80.6 (C2'), 77.8 (C3'), 69.9 (C4'), 35.3 (C5'); *isopropylidene*: 113.5 (C), 26.9 (CH_{3a}), 25.1 (CH_{3b}).

Compound 12: R_f = 0.27 (CHCl₃/EtOH: 9/1); ¹H NMR (DMSO *d*₆): *adenine*: 8.28 (s, 1H, H₈), 8.19 (s, 1H, H₂), 7.36 (s, NH₂); *ose*: 6.23 (d, 1H, J = 2.0 Hz, H_{1'}), 5.45 (dd, 1H, J = 2.0 Hz, J = 6.2 Hz, H_{2'}), 5.15 (dd, 1H, J = 3.4 Hz, J = 6.2 Hz, H_{3'}), 4.77 (dd, 1H, J = 5.4 Hz, J = 14.1 Hz, H_{5'b}), 4.67 (dd, 1H, J = 7.7 Hz, 14.1 Hz, H_{5'a}), 4.55 (m, 1H, H_{4'}); *isopropylidene*: 1.53 (s, 3H, CH_{3b}), 1.31 (s, 1H, CH_{3a}); *linker*: 7.95 (s, 1H, H_{triazole}), 4.47 (d, 2H, J = 12.4, CH_{2triazole}); *thymine*: 11.31 (s, 1H, NH), 7.39 (s, 1H, H₆), 1.77 (s, 3H, CH₃); *ose*: 6.08 (d, 1H, J = 6.8 Hz, J = 7.4 Hz, H_{1'}), 4.26 (dd, 1H, J = 3.5 Hz, J = 10.9 Hz, H_{5'b}), 4.20 (dd, 1H, J = 5.5 Hz, J = 10.9 Hz, H_{5'a}), 4.13 (ddd, 1H, J = 3.0 Hz, J = 5.5 Hz, J = 6.0 Hz, H_{3'}), 4.06 (ddd, 1H, J = 3.2 Hz, J = 5.4 Hz, J = 6.2 Hz, H_{4'}), 2.19 (m, 1H, H_{2'}); *tosyl*: 7.78 (d, 2H, J = 8.2 Hz, H_{ortho/S}), 7.45 (d, 2H, J = 8.2 Hz, H_{meta/S}), 2.39 (s, 3H, CH₃); ¹³C NMR (DMSO *d*₆): *adenine*: 156.2 (C6), 152.8 (C2), 148.6 (C4), 140.1 (C8), 119.2 (C5); *ose*: 89.0 (C1'), 84.5 (C4'), 83.3 (C2'), 81.5 (C3'), 51.0 (C5'); *isopropylidene*: 113.7 (C), 26.9 (CH_{3a}), 25.2 (CH_{3b}); *linker*: 143.5 (C_{triazole}), 124.5 (CH_{triazole}), 62.0 (CH_{2triazole}); *thymine*: 163.6 (C4), 150.3 (C2), 135.9 (C6), 109.9 (C5); *ose*: 84.3 (C1'), 80.8 (C4'), 78.2 (C3'), 70.1 (C5'), 35.6 (C2'), 12.1 (CH₃); *tosyl*: 145.1 (C_{p/S}), 132.1 (C_{ipso/S}), 130.2 (C_{m/S}), 127.6 (C_{o/S}), 21.1 (CH₃).

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