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Synthesis of 2*S*-(2-hydroxyethyl)-3*R*-hydroxy-4*S*-(thymin-1-yl or adenin-9-yl)-tetrahydrofuran

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ABSTRACT

Two synthetic strategies were developed to obtain isonucleosides **2a** and **2b**. Starting from the known compound **4**, an extension of one carbon unit at sugar 6-terminal was achieved by Wittig reaction and Stannyl-desulfonylation reaction. After oxidation of the double bond, the isonucleosides with elongated side chain **2a** and **2b** were synthesized. For the synthesis of isonucleosides containing different bases, an epoxide intermediate approach was developed. Isonucleosides **2a** and **2b** were synthesized by regioselective epoxide opening reaction of **18** in good yield.

1. Introduction

As a class of potential therapeutic agents, antisense oligonucleotides have been developed for the treatment of diseases such as cancer, inflammation, and virus infection.[1–4] However, several drawbacks that have emerged negatively affect their therapeutic efficacy. For example, natural oligodeoxynucleotides are readily degraded in the serum or in vivo and show poor uptake by the cell membrane. To improve the biostability of oligonucleotides, chemically modified oligonucleotides are widely used. Though phosphorothioate oligodeoxynucleotides are currently used as the standard choice of chemically modified oligodeoxynucleotides, its non-sequence-specific protein binding leads to significant side effects, including complement activation, thrombocytopenia, inhibition of cell–matrix interaction, and reduction of cell proliferation.[5] To overcome these limitations, intensive efforts were focused on the development of other kinds of chemically modified oligonucleotides, which were named as the second generation of oligonucleotides. For example, modifications of the 2-position of ribose with electronegative substituents such as the 2′-*O*-(2-methoxy)ethyl (MOE) group[6] or a 2′-*O*,4′-*C*-methylene bridge (locked nucleic acid; LNA) were performed.[7]

Isonucleosides represent a novel class of nucleoside analogues in which the nucleobase is linked to various positions of ribose other than C-1 (Fig. 1). Because of the shift of *N*-glycosidic bond from 1′- to 2′-position, the chemical and enzymatic stabilities of the nucleosides increase. Previous studies in our group showed that homo-oligoisonucleotides antagonized the hydrolysis of snake venom phosphodiesterase. Furthermore, some kinds of homo-oligoisonucleotides also showed strong binding abilities to their complementary sequences though they were a little weaker than the native counterpart[8–12] (Fig. 1, I and II). The results suggested that antisense oligonucleotides constructed from isonucleotides could antagonize the hydrolysis of nuclease and showed acceptable binding abilities, maintained the inhibitory abilities to decrease mRNA transcription and functional protein translation.[12] The further modification of compound **II** (R=CH_2OH, Fig. 1) gave amino-isonucleosides, which were successfully incorporated into siRNA and increased the gene silencing efficiency of siRNA when they were incorporated at sense strand of siRNA.[13]

To investigate whether the extension of phosphodiester linkage could improve the hybridization properties, we reported previously the synthesis of 1′,4′-anhydro-2′,5′-dideoxy-2′-nucleobase-D-altritol (**1**) in which an additional methylene group was introduced at the 6-position of sugar moiety of compound **I** (R=H).[14] (Fig. 1) It was found that oligomers containing **1** could form duplexes with both DNA and RNA complementary strands, which indicated that the extended phosphodiester linkage in these oligomers rendered the sugar moiety more flexible to fit the required A or B conformation of the duplex.[15] In order to investigate the hybridization properties of oligonucleotides consisting of the isonucleosides with elongated side chain, we report here the synthesis of 2*S*-(2-hydroxyethyl)-3*R*-hydroxy-4*S*-(thymin-1-yl or adenin-9-yl)-tetrahydrofuran (**2**), the enantiomer of **1**.

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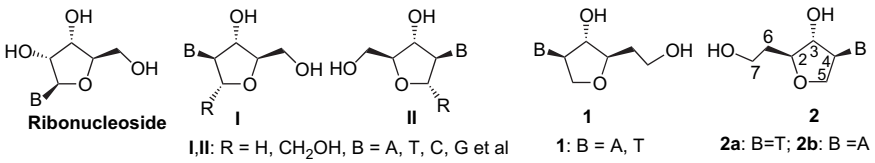
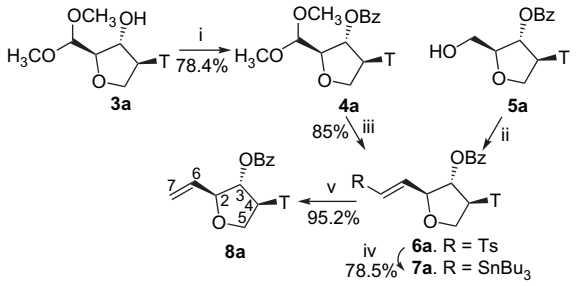


Figure 1. Structures of ribonucleoside and isonucleosides.

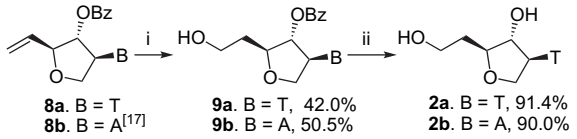
2. Results and discussion

In our reported works, compound **1** was synthesized from D-glucose by 11 synthetic steps.[13] Compound **2** could be obtained from L-glucose. However, L-glucose is not a convenient starting material. In this paper we present the synthesis of isonucleoside **2** from D-xylose by two concise approaches. According to the retrosynthesis analysis, compound **2** could be obtained from compound **II** (Fig. 1, R=H) by extension of one carbon unit at 6-terminal. Therefore, the known compound **5a**[16] was oxidized and followed by Wittig reaction and stannyl-desulfonylation[17] to yield the key intermediate **7a**. However, it was found that the key intermediate **7** could be yielded directly from compound **4a**, which was prepared from compound **3a**.[16] The acetal group in compound **4a** was hydrolyzed by 1% HCl and reacted with Wittig reagent in one-pot to give compound **6a** in 85.0% yield. Compound **6a** was then reacted with Bu_3SnH and AIBN to yield compound **7a** (Scheme 1).



Scheme 1. Reagents and conditions: (i) BzCl, Py; (ii) (a) DCC, DMSO, $Cl_2CHCOOH$; (b) $TsCH{=}PPh_3$; (iii) (a) 1% HCl, THF, 70–90 °C; (b) DMSO, $TsCH{=}PPh_3$; (iv) Bu_3SnH, AIBN, toluene, reflux; (v) NH_4F, EtOH, reflux.

Destannylation of **7a** with ammonium fluoride in ethanol at 80 °C gave compound **8a**. Compound **8a** or **8b**[17] was hydroborated first by borane-dimethyl sulfide complex then reacted with hydrogen peroxide to give compound **9a** or **9b** in 42.0 or 50.5% yield and some debenzoylated product **2a** or **2b** in ~17.0% yield. Compound **9a** or **9b** can be converted completely to **2a** or **2b** using $NaOCH_3$ in 91.4 or 90.0% yield, respectively (Scheme 2).



Scheme 2. Reagents and conditions: (i) (a) BH_3-SMe_2, THF, 2 N NaOH, 30% H_2O_2; (ii) $NaOCH_3$, MeOH.

In another approach, the formation of *N*-glycoside was postponed to the later synthetic step. By this strategy, an epoxide intermediate **18** was synthesized. From this intermediate, various base substituted isonucleosides can be prepared more easily. As shown in Scheme 3, compound **10**[18] was protected to give benzoate **11** in which the acetal group was hydrolyzed by trifluoroacetic acid in water to yield aldehyde **12** quickly and completely. Without purification, crude **12** was reacted with Wittig reagent [(*p*-tolylsulfonyl)methylene]triphenylphosphorane to give compound **13** (*E*-isomer and minor *Z*-isomer, without separation) in 71.0% yield. Stannyl-desulfonylation of **13** with Bu_3SnH in toluene, followed by treatment with NH_4F in EtOH at 90 °C, afforded compound **15** in 60.0% yield.

Compound **15** was hydroborated using 9-BBN (1 M solution in THF) and subsequently oxidized by H_2O_2 to give compound **16**. In this reaction, 0.5 M NaOH was used to ensure the benzoate stable. Crude **16** was protected by *tert*-butyldimethylsilyl group. The key intermediate epoxide **18** was successfully obtained by intramolecular nucleophilic attack under basic condition.

The regioselective attack of epoxide **18** by thymine or adenine was accomplished using DBU as a basic catalyst. The desired and predominant compound **19a** (35.5% yield) and **19b** (46.8% yield) was obtained along with a small amount of regioisomer **20a** (about 4.0% yield) and **20b** (about 5.0% yield), respectively. Compound **19a** or **19b** was deprotected using 1 M TBAF solution in THF to obtain **2a** (65.5% yield) or **2b** (61.4% yield), respectively.

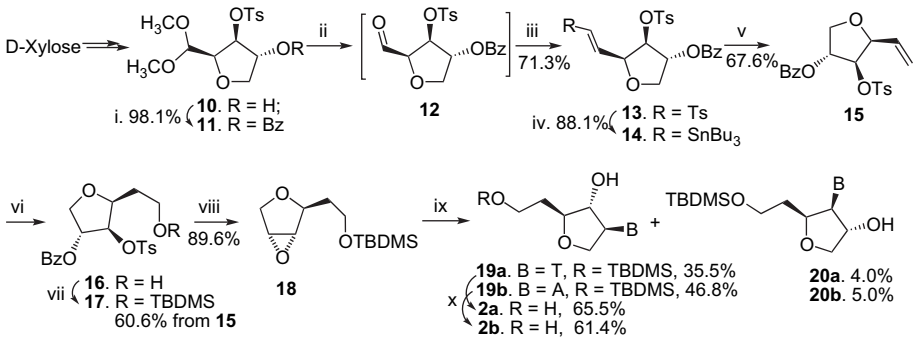
There were no differences for the general data (NMR, optical rotation, MS, and UV) of compound **2a** or **2b** obtained from two different methods, respectively. The structure of **2b** was characterized further by ^1H NMR, ^1H–^1H COSY, and NOESY spectra. The strong NOE effect of 3-OH with 2-H and 4-H in sugar moiety confirms that adenine and 2-(2-hydroxyethyl) group are on the same side of the sugar ring, and adenin-9-yl is connected at 4-position of sugar moiety (Fig. 2).[19]

In conclusion, two synthetic strategies were developed to synthesize isonucleosides **2a** and **2b**. Starting from the known compound **4**, an extension of one carbon unit at sugar 6-terminal was achieved by Wittig reaction and Stannyl-desulfonylation reaction. After oxidation of the double bond, the isonucleosides with elongated side chain **2a** and **2b** were synthesized. For the synthesis of isonucleosides containing different bases, an approach with epoxide intermediate **18** was designed. Isonucleosides **2a** and **2b** were synthesized by regioselective epoxide opening reaction in good yield. The preliminary results showed that compound **2a** or **2b** incorporated antisense oligonucleotides (single incorporation at 3′-end, 5′-end or middle of single strand) kept almost same affinity to complementary strand as that of **II** (R=H, B=A, T), and all were lower than that of natural one. The further results will be reported elsewhere.[20]

3. Experimental

3.1. General

All solvents were dried and distilled prior to use. Chemical reagents were purchased from Acros and Sigma Co., and were used without further purification. Thin layer chromatography was performed on silica gel GF_{254} (Qin-Dao Chemical Co., China) plates with detection by UV or by heating. Silica gel (200–300 mesh; Qin-Dao Chemical Co.) was used for short column chromatography. NMR spectra were recorded on JEOL JNM-AL300 or Varian INOVA-500 instrument. ^1H NMR and ^{13}C NMR spectra were referenced using DMSO-d_6 or $CDCl_3$ as a solvent with internal standard TMS. Elemental analyses were performed by using a Vario EL III instrument. High-resolution ESI mass spectra were obtained at MDS



Scheme 3. Reagents and conditions: (i) BzCl, DMAP, Py; (ii) TFA/H_2O (v/v=7:1), rt; (iii) Ph_3P=CHTs, THF; (iv) Bu_3SnH, AIBN, $PhCH_3$; (v) NH_4F, EtOH; (vi) (a) BH_3-THF; (b) 0.5 N NaOH, 30% H_2O_2; (vii) TBDMSCl, DMF, imidazole; (viii) K_2CO_3, MeOH; (ix) adenine, DBU, DMF; (x) TBAF, THF.

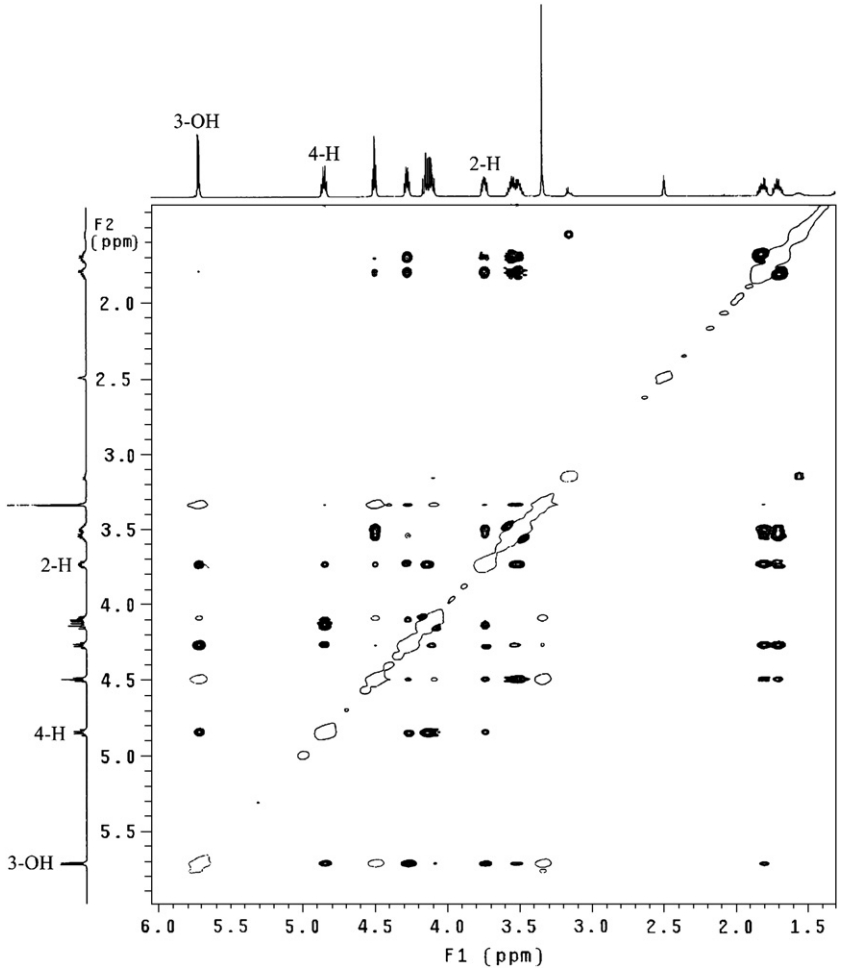


Figure 2. NOE spectrum of compound **2b**. The NOE exist between 2-H, 3-OH, and 4-H, respectively.

SCIEX QSTAR and Bruker DALTONICS APEX IV 70e instruments, and the data are reported in *m*/*e* (intensity to 100%). Optical rotations were recorded on Perkin–Elmer 243B Polarimeter.

*3.1.1. [2R-Dimethoxymethyl-3R-benzoxy-4S-(thymin-1-yl)]-tetrahydrofuran (**4a**)*

To a solution of **3a**[15] (1.4 g, 4.9 mmol) in dry pyridine, BzCl (0.84 mL, 7.35 mmol) was added and the mixture was stirred for 4 h at room temperature. After evaporation, the residue was dissolved in EtOAc, washed with satd $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to yield **4a** (1.5 g, 78.4%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85 (s, 3H, T-CH_3), 3.42 (s, 3H, –OCH_3), 3.45 (s, 3H, –OCH_3), 4.01 (dd, 1H, $J_{5a,4}$=2.7 Hz, $J_{5a,5b}$=10.5 Hz, 5a-H), 4.08 (dd, 1H, $J_{2,6}$=3.3 Hz, 2-H), 4.17 (dd, 1H, $J_{5b,4}$=6.9 Hz, 5b-H), 4.65 (d, 1H, 6-H), 5.25 (t, 1H, $J_{2,3}$=3.0 Hz, 3-H), 5.49 (d, 1H, $J_{3,4}$=3.0 Hz, 4-H), 7.32–7.60 (m, 3H, Bz), 7.49 (s, 1H, 6-H in thymine), 7.94 (d, 2H, Bz-H), 10.02 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 56.0, 56.8, 60.9, 71.5, 78.8, 83.5, 104.1, 111.4, 128.4, 129.8, 128.9, 133.5, 137.4, 150.8, 163.8, 165.6; HRMS (TOF) calcd for $C_{19}H_{23}N_2O_7$ $(M+H)^+$: 391.1499, found: 391.1489.

*3.1.2. {2S-[2(E)-p-Tolunenesulfonylethylene]}-3R-benzoxy-4S-(thymin-1′-yl)}-tetrahydrofuran (**6a**)*

Compound **4a** (400 mg, 1.02 mmol) was dissolved in the mixture of THF (7 mL) and 1% HCl solution (7 mL), and the solution was stirred for 2 days at 70 °C. NaOH (2 N) was used to neutralize the solution to pH=7 and the mixture was extracted with CH_2Cl_2. The organic layer was washed with satd $NaHCO_3$ solution, brine, dried over anhydrous Na_2SO_4 and $CuSO_4$, and then concentrated to yellow syrup. The crude syrup was dissolved in DMSO (3.5 mL) under an inert atmosphere and [(*p*-tolylsulfonyl)methylene]-triphenylphosphorane (620 mg, 1.45 mmol) was added. The mixture was stirred overnight at room temperature. MeOH (8 mL) was added and stirred for 30 min at room temperature, the resulting mixture was filtered and washed with cold MeOH, and the combined filtrates were evaporated. The residue was partitioned (EtOAc/H_2O), the organic layer was washed with H_2O (three times), $NaHCO_3$ solution, and brine, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to give **6a** (453 mg, 80.0%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (s, 3H, T-CH_3), 2.44 (s, 3H, Ts-CH_3), 4.17 (dd, 1H, $J_{5a,4}$=3.3 Hz, $J_{5a,5b}$=10.5 Hz, 5a-H), 4.32 (dd, 1H, $J_{5b,4}$=6.6 Hz, 5b-H), 5.22 (dd, 1H, $J_{2,3}$=5.7 Hz, 3-H), 4.65 (dt, 1H, $J_{2,6}$=2.1 Hz, 2-H), 5.34 (dt, 1H, $J_{3,4}$=3.0 Hz, 4-H), 6.77 (dd, 1H, $J_{6,7}$=15.0 Hz, 6-H), 7.01 (s, 1H, 6-H in thymine), 7.27 (d, 1H, $J_{6,7}$=15.0 Hz 7-H), 7.43–7.71 (m, 5H, Bz), 7.79 (d, 2H, Ts), 8.02 (d, 2H, Ts), 8.32 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 21.6, 60.9, 70.8, 81.5, 82.0, 112.5, 127.9, 128.4, 128.5, 128.6, 129.9, 130.1, 131.9, 132.0, 132.1, 132.8, 134.1, 135.8, 139.7, 144.9, 150.3, 162.9, 165.7; HRMS (TOF) calcd for $C_{25}H_{23}N_2O_7S$ $(M-H)^+$: 495.1231, found: 495.1208.

*3.1.3. {2S-[2(E)-Tributylstannylvinyl]}-3R-benzoxy-4S-(thymin-1-yl)}-tetrahydrofuran (**7a**)*

To a solution of **6a** (130 mg, 0.262 mmol) in toluene (10 mL), Bu_3SnH (0.25 mL, 0.825 mmol) was added under the atmosphere of argon. After 15 min, AIBN (11 mg, 0.052 mmol) was added. The solution was refluxed for 4 h, evaporated, and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to yield **7a** (130 mg, 78.5%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, 9H, butyl–CH_2–CH_3), 0.91 (t, 6H, butyl–CH_2–), 1.20–1.31 (m, 6H, butyl–CH_2–), 1.42–1.54 (m, 6H, butyl–CH_2–), 1.94 (s, 3H, T-CH_3), 4.07 (dd, 1H, $J_{5a,4}$=3.0 Hz, $J_{5a,5b}$=10.5 Hz, 5a-H), 4.31 (dd, 1H, $J_{5b,4}$=7.0 Hz, 5b-H), 4.40–4.43 (m, 1H, $J_{2,6}$=5.0 Hz, 2-H), 5.20 (dd, 1H, $J_{2,3}$=6.0 Hz, 3-H), 5.33 (m, 1H, $J_{3,4}$=3.0 Hz, 4-H), 6.21 (dd, 1H, $J_{6,7}$=19.0 Hz, 6-H), 6.52 (d, 1H, 7-H), 7.27 (s, 1H, 6-H in thymine), 7.47 (t, 2H, Bz), 7.60 (t, 1H, Bz), 8.02 (d, 2H, Bz), 8.06 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.5, 12.6, 13.6, 27.2, 29.0, 30.9, 60.8, 70.7, 82.3, 85.8, 112.0, 128.5, 128.9, 129.8, 133.6, 133.8, 136.4, 142.3, 150.4, 163.0, 165.4; HRMS (TOF) calcd for $C_{30}H_{45}N_2O_5Sn$ $(M+H)^+$: 633.2344, found: 633.2373.

*3.1.4. [2S-(1-Vinyl)-3R-benzoxy-4S-(thymin-1-yl)]-tetrahydrofuran (**8a**)*

To a solution of **7a** (250 mg, 0.395 mmol) in dry EtOH (50 mL), NH_4F (650 mg, 19.7 mmol) was added and the resulting solution was refluxed for 3 days, and then evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to give **8a** (129 mg, 95.2%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87 (s, 3H, thymine-CH_3), 4.02 (dd, 1H, $J_{5a,4}$=2.7 Hz, $J_{5a,5b}$=10.5 Hz, 5a-H), 4.23 (dd, 1H, $J_{5b,4}$=6.9 Hz, 5b-H), 4.36–4.40 (m, 1H, 2-H), 5.13 (dd, 1H, $J_{2,3}$=6.0 Hz, 3-H), 5.26–5.31 (m, 2H, 4-H, 7a-H), 5.42–5.45 (m, 1H, 7b-H), 6.04 (dd, 1H, $J_{6,7}$=17.8, 5.28 Hz, 6-H), 7.19 (s, 1H, 6-H in thymine), 7.38 (t, 2H, Bz-H), 7.53 (t, 1H, Bz-H), 7.96 (d, 2H, Bz-H), 8.90 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 61.0, 70.9, 81.5, 82.4, 112.2, 118.4, 128.6, 128.8, 129.9, 133.7, 136.7, 136.4, 150.4, 163.0, 165.7; HRMS (TOF) calcd for $C_{18}H_{19}N_2O_5$ $(M+H)^+$: 343.1288, found: 343.1287.

*3.1.5. [2S-(1-Vinyl)-3R-benzoxy-4S-(adenin-9-yl)]-tetrahydrofuran (**8b**)*

Compound **8b** was synthesized by the reported method.[17]

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.32 (d, 1H, $J_{5,4}$=2.7 Hz, 5b-H), 4.43 (dd, 1H, $J_{5,4}$=5.7, 10.5 Hz, 5a-H), 4.59 (d, 1H, $J_{3,2}$=4.5 Hz, 3-H), 5.20–5.39 (m, 2H, 7-H), 5.33 (d, 1H, $J_{4,3}$=7.8 Hz, 4-H), 5.48 (d, 1H, $J_{2,3}$=4.5 Hz, 2-H), 5.70 (6-NH_2 in adenine), 6.25 (s, 1H, 6-H), 7.55–8.06 (m, 5H, Bz), 8.01(s, 1H, H-2 in adenine), 8.39 (s, 1H, H-8 in adenine).

*3.1.6. [2S-(2-Hydroxyethyl)-3R-benzoxy-4S-(thymin-1-yl)]-tetrahydrofuran (**9a**)*

To a solution of **8a** (90 mg, 0.26 mmol) in anhydrous THF (10 mL), BH_3-SMe_2 complex (1 M solution in THF, 0.47 mL, 0.46 mmol) was added under an inert atmosphere. The reaction was stirred for 2 h at room temperature and then cooled to 0 °C, 2 N NaOH (1.54 mL, 0.304 mmol) and 30% H_2O_2 (0.55 mL, 0.456 mmol) were added. After stirring for another 2 h at room temperature, the mixture was concentrated. The complex was dissolved in $CHCl_3$ and washed with water and satd $NaHCO_3$, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified by silica gel column chromatography (cyclohexane/EtOAc) to give **9a** (39 mg, 42%) and **2a** (11 mg, 17%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80 (d, 3H, thymine-CH_3), 1.83–1.99 (m, 2H, 6-H), 3.97–4.02 (m, 2H, 7-H), 4.04 (dd, $J_{5a,4}$=4.5 Hz, $J_{5a,5b}$=10.0 Hz, 1H, 5a-H), 4.07–4.11 (m, 1H, 2-H), 4.13 (dd, $J_{5b,4}$=2.5 Hz, 1H, 5b-H), 4.52 (br s, 1H, –OH), 5.06–5.11 (m, 1H, 3-H), 5.28–5.32 (m, 1H, 4-H), 7.52 (d, J=1.0 Hz, 1H, 6-H in thymine), 7.54–7.57 (m, 2H, Bz-H), 7.65–7.75 (m, 3H, Bz-H), 11.30 (br s, 1H, –NH–); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2, 35.2, 57.3, 61.5, 68.6, 79.2, 81.3, 109.6, 128.8, 129.4, 131.5, 134.0, 137.7, 150.8, 163.8; HRMS (TOF) calcd for $C_{18}H_{21}N_2O_6$ $(M+H)^+$: 361.1394, found: 361.1397.

*3.1.7. [2S-(2-Hydroxyethyl)-3R-benzoxy-4S-(adenin-9-yl)]-tetrahydrofuran (**9b**)*

By the same method as that for **9a**, **9b** was obtained from **8b** in 50.5% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.84–2.01 (m, 2H, 6-H), 3.98–4.02 (m, 2H, 7-H), 4.03 (dd, $J_{5a,4}$=4.5 Hz, $J_{5a,5b}$=10.0 Hz, 1H, 5a-H), 4.05–4.09 (m, 1H, 2-H), 4.14 (dd, $J_{5b,4}$=2.5 Hz, 1H, 5b-H), 4.53 (br s, 1H, 3-OH), 5.06–5.10 (m, 1H, 3-H), 5.30–5.35 (m, 1H, 4-H), 5.71 (6-NH_2 in adenine), 7.54–7.58 (m, 2H, Bz-H), 7.65–7.9 (m, 3H, Bz-H), 8.01 (s, 1H, H-2 in adenine), 8.28 (s, 1H, H-8 in adenine).

*3.1.8. {2S-[2-Hydroxyethyl]-3R-hydroxyl-4S-(thymin-1-yl)}-tetrahydrofuran (**2a**)*

To the solution of **9** (20 mg, 0.055 mmol) in anhydrous MeOH (10 mL), 30% NaOMe in MeOH (0.15 mL) was added. The mixture was stirred at room temperature for 1 h and evaporated. The residue was purified by silica gel chromatography (CH_2Cl_2/MeOH) to give **2a** (13 mg, 91.4%) as a white solid.

$[\alpha]_D^{20}$ +8.39 (*c* 0.155, MeOH); UV (MeOH): λ_{max}=271 nm (ε 8600). ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.92 (s, 3H, thymine-CH_3), 1.88–2.05 (m, 2H, 6-H), 3.63–3.87 (m, 2H, 7-H), 3.88–3.92 (m, 1H, 2-H), 4.01 (dd, 1H, $J_{5a,4}$=2.7 Hz, $J_{5a,5b}$=10.5 Hz, 5a-H), 4.04–4.09 (m, 1H, 3-H), 4.19 (dd, 1H, $J_{5b,4}$=6.9 Hz, 5b-H), 4.51 (t, J=5.0 Hz, 1H, 7-OH), 4.95–4.99 (m, 1H, $J_{3,4}$=6.6 Hz, 4-H), 5.73 (d, J=5.5 Hz, 1H, 3-OH), 7.27 (s, 1H, 6-H in thymine), 9.39 (br s, 1H, –NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.1, 35.8, 57.7, 62.4, 68.2, 78.7, 80.4, 109.5, 137.7, 151.1, 163.8; HRMS (TOF) calcd for $C_{12}H_{17}N_2O_5$ $(M+H)^+$: 257.1137, found: 257.1140.

*3.1.9. {2S-[2-Hydroxyethyl]-3R-hydroxyl-4S-(adenin-1-yl)}-tetrahydrofuran (**2b**)*

$[\alpha]_D^{20}$ +41.07 (*c* 0.056, MeOH); UV (MeOH): λ_{max}=260.5 nm (ε 12,250). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.68–1.75 (m, 1H, 6-H),

1.79–1.86 (m, 1H, 6-H), 3.35–3.60 (m, 2H, 7-H), 3.73–3.77 (m, 1H, 2-H), 4.12 (dd, $J_{5a,5b}$=9.5 Hz, $J_{5a,4}$=1.0 Hz, 1H, 5a-H), 4.16 (dd, $J_{5b,4}$=2.0 Hz, 1H, 5b-H), 4.27–4.31 (m, 1H, 3-H), 4.51 (t, J=5.0 Hz, 1H, 7-OH), 4.84–4.88 (m, 1H, 4-H), 5.73 (d, J=5.5 Hz, 1H, 3-OH), 7.25 (s, 2H, $-NH_2$), 8.16 (s, 1H, 2-H in adenine), 8.17 (s, 1H, 8-H in adenine); ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.2, 57.7, 61.8, 68.7, 79.0, 81.0, 119.0, 139.3, 149.5, 152.4, 156.0. Anal. Calcd for $C_{11}H_{15}N_5O_3$: C, 49.81; H, 5.70; N, 26.40. Found: C, 50.01; H, 6.00; N, 26.33.

3.1.10. [2R-Dimethoxymethyl-3S-p-toluenesulfonyl-4R-benzoxy]-tetrahydrofuran (**11**)

To the solution of **10**[18] (1.99 g, 5.99 mmol) in dry pyridine (40 mL), BzCl (1.05 mL, 9.11 mmol) and DMAP (77 mg, 0.63 mmol) were added. The reaction mixture was stirred at room temperature overnight and then evaporated. The residue was dissolved in EtOAc, washed with satd $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to give **11** (2.56 g, 98.1%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 3H, Ts-CH_3), 3.32 (s, 3H, $-OCH_3$), 3.46 (s, 3H, $-OCH_3$), 3.90 (dd, $J_{5a,5b}$=11.0 Hz, $J_{5a,4}$=2.5 Hz, 1H, 5a-H), 4.15 (dd, $J_{2,3}$=3.5 Hz, $J_{2,6}$=7.0 Hz, 1H, 2-H), 4.37 (dd, $J_{5b,4}$=5.0 Hz, 1H, 5b-H), 4.53 (d, 1H, 6-H), 5.15 (dd, $J_{3,4}$=1.0 Hz, $J_{2,3}$=3.5 Hz, 1H, 3-H), 5.35–5.36 (m, 1H, 4-H), 7.35 (d, 2H, Bz), 7.43–7.47 (m, 2H, Bz-H), 7.58–7.60 (m, 1H, Bz-H), 7.88 (d, 2H, Ts), 7.96–7.98 (m, 2H, Ts); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 53.9, 55.5, 71.9, 76.9, 79.2, 82.3, 101.9, 128.0, 128.4, 128.8, 129.7, 129.9, 133.3, 133.6, 145.3, 164.8. Anal. Calcd for $C_{21}H_{24}O_8S$: C, 57.79; H, 5.54. Found: C, 57.54; H, 5.46.

3.1.11. {2S-[2(E)-p-Toluenesulfonylethylene]-3R-p-toluenesulfonyl-4R-benzoxy}-tetrahydrofuran (**13**)

Compound **11** (440 mg, 1.01 mmol) was dissolved in trifluoroacetic acid (3.5 mL) and water (0.5 mL). The solution was stirred for 5 h at room temperature. After evaporation of most solvents, the residue was dissolved in CH_2Cl_2, washed with satd $NaHCO_3$ and brine, and dried over Na_2SO_4. Solvents were removed to afford white foam (crude **12**). To a solution of crude **12** in anhydrous THF (10 mL), [(*p*-tolylsulfonyl)methylene]triphenylphosphorane (475 mg, 1.10 mmol) was added and the mixture was stirred for 20 h at room temperature. Saturated NH_4Cl solution was added to quench the reaction and the aqueous system was thoroughly extracted with EtOAc. After drying over Na_2SO_4, the organic extracts were evaporated and the residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to yield **13** (390 mg, 71.3%) as a white foam.

$[\alpha]_D^{20}$ −97.50 (*c* 0.040, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.44 (s, 6H, Ts-CH_3), 3.92 (dd, $J_{5a,5b}$=11.0 Hz, $J_{5a,4}$=2.0 Hz, 1H, 5a-H), 4.34 (dd, $J_{5b,4}$=4.5 Hz, 1H, 5b-H), 4.82–4.84 (m, 1H, 2-H), 5.13 (dd, $J_{3,4}$=1.5 Hz, $J_{2,3}$=4.0 Hz, 1H, 3-H), 5.40–5.41 (m, 1H, 4-H), 6.79 (dd, $J_{6,7}$=15 Hz, $J_{2,7}$=1.5 Hz, 1H, 7-H), 6.81 (dd, $J_{2,6}$=4.0 Hz, 1H, 6-H), 7.34–7.38 (m, 4H, Ts, Bz), 7.44–7.47 (m, 2H, Bz), 7.59–7.62 (m, 1H, Bz), 7.78–7.84 (m, 4H, Ts), 7.95–7.96 (m, 2H, Ts); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 21.7, 71.6, 77.3, 78.2, 81.5, 128.0, 128.1, 128.6, 128.7, 129.8, 130.0, 130.3, 132.4, 133.7, 133.8, 136.8, 137.5, 144.6, 145.8, 164.8. Anal. Calcd for $C_{27}H_{26}O_8S_2$: C, 59.76; H, 4.83. Found: C, 59.90; H, 5.02.

3.1.12. {2S-[2(E)-Tributylstannylvinyl]-3R-p-toluenesulfonyl-4R-benzoxy}-tetrahydrofuran (**14**)

To a solution of **13** (1.68 g, 3.10 mmol) and AIBN (118 mg, 0.71 mmol) in toluene (40 mL), Bu_3SnH (2.7 mL, 9.7 mmol) was added under an inert atmosphere. The reaction mixture was refluxed for 5 h and then evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to give **14** (1.85 g, 88.1%) as a colorless syrup.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88–0.93 (m, 15H, butyl–CH_2–CH_3), 1.28–1.36 (m, 6H, butyl–CH_2–), 1.48–1.54 (m, 6H, butyl–CH_2–), 2.39 (s, 3H, Ts-CH_3), 3.83 (dd, $J_{5a,5b}$=10.5 Hz, $J_{5a,4}$=2.5 Hz, 1H, 5a-H), 4.40 (dd, $J_{5b,4}$=5.5 Hz, 1H, 5b-H), 4.55–4.57 (m, 1H, 2-H), 5.08 (dd, $J_{3,4}$=2.0 Hz, $J_{2,3}$=4.0 Hz, 1H, 3-H), 5.39–5.40 (m, 1H, 4-H), 6.00 (dd, $J_{2,6}$=6.0 Hz, $J_{6,7}$=19 Hz, 1H, 6-H), 6.44 (dd, $J_{2,7}$=1.0 Hz, 1H, 7-H), 7.29–7.32 (m, 2H, Bz), 7.44–7.48 (m, 2H, Bz), 7.58–7.64 (m, 1H, Bz), 7.81–7.84 (m, 2H, Ts), 7.96–8.00 (m, 2H, Ts); ^{13}C NMR (125 MHz, $CDCl_3$): δ 9.4, 10.7, 13.6, 21.6, 27.2, 29.0, 71.1, 77.7, 83.1, 127.9, 128.1, 128.4, 129.0, 129.7, 129.8, 133.5, 136.0, 139.7, 145.1, 165.0. Anal. Calcd for $C_{32}H_{46}O_6SSn$: C, 56.73; H, 6.84. Found: C, 56.87; H, 6.80.

3.1.13. [2S-2-Vinyl-3R-p-toluenesulfonyl-4R-benzoxy]-tetrahydrofuran (**15**)

To the solution of **14** (129 mg, 0.19 mmol) in dry EtOH (6 mL), NH_4F (331 mg, 10.03 mmol) was added and the resulting solution was refluxed for 28 h and then evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to yield **15** (50 mg, 67.6%) as a white solid.

$[\alpha]_D^{20}$ −1.25 (*c* 0.400, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.40 (s, 3H, Ts-CH_3), 3.84 (dd, $J_{5a,5b}$=10.5 Hz, $J_{5a,4}$=3.0 Hz, 1H, 5a-H), 4.39 (dd, $J_{5b,4}$=4.5 Hz, 1H, 5b-H), 4.56–4.59 (m, 1H, 2-H), 5.07 (dd, $J_{3,4}$=4.0 Hz, $J_{2,3}$=1.5 Hz, 1H, 3-H), 5.28–5.30 (m, $J_{7a,7b}$=1.5 Hz, $J_{7a,6}$=10.5 Hz, 1H, 7a-H), 5.36–5.42 (m, 2H, 4-H, 7b-H), 5.80–5.80 (m, $J_{7b,6}$=17.0 Hz, 1H, 6-H), 7.30–7.32 (d, 2H, Bz), 7.44–7.48 (m, 2H, Bz), 7.59–7.62 (m, 1H, Bz), 7.82–7.84 (d, 2H, Ts), 7.96–7.99 (m, 2H, Ts); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 71.2, 77.7, 80.9, 83.3, 119.9, 128.0, 128.5, 128.9, 129.7, 129.9, 130.9, 133.2, 133.6, 145.3, 165.0. Anal. Calcd for $C_{20}H_{20}O_6S$: C, 61.84; H, 5.19. Found: C, 61.70; H, 5.32.

3.1.14. {2S-[2-O-tert-Butyldimethylsilyl-ethyl]-3R-p-toluenesulfonyl-4R-benzoxy}-tetrahydrofuran (**17**)

To a solution of **15** (169 mg, 0.435 mmol) in anhydrous THF (3.5 mL), 9-BBN (0.5 M in THF, 4.5 mL, 2.25 mmol) was added under an inert atmosphere. The mixture was stirred for 3 h at room temperature and then H_2O (1 mL), 0.5 M NaOH solution (15.8 mL, 7.9 mmol), and 30% H_2O_2 (3.05 mL, 30.32 mmol) were added. After the mixture was kept stirring for another 3 h at 0 °C, satd NH_4Cl solution was added to quench the reaction. The aqueous system was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and then evaporated. The residue was purified quickly by silica gel column chromatography (petroleum ether/EtOAc) to give crude **16**. To the solution of crude **16** in dry DMF (3.5 mL), TBDMSCl (69 mg, 0.46 mmol) and imidazole (76 mg, 1.11 mmol) were added and the mixture was stirred for 2 h at room temperature. Water was added to quench the reaction and the solvent was evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to yield **17** (137 mg, 60.6%) as a colorless syrup.

$[\alpha]_D^{20}$ −73.08 (*c* 0.026, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (s, 6H, TBDMS-CH_3), 0.88 (s, 9H, TBDMS-^{t}Bu), 1.74–1.80 (m, 1H, $-CH_2-$), 1.86–1.93 (m, 1H, $-CH_2-$), 2.38 (s, 3H, Ts-CH_3), 3.66–3.75 (m, 3H, 5a-H, $-CH_2-O-$), 4.27–4.30 (m, 1H, 2-H), 4.34 (dd, $J_{5a,5b}$=10.5 Hz, $J_{5b,4}$=5.5 Hz, 1H, 5b-H), 5.03 (dd, $J_{3,4}$=1.0 Hz, $J_{2,3}$=4.0 Hz, 1H, 3-H), 5.30–5.32 (m, 1H, 4-H), 7.31 (d, 2H, Bz-H), 7.43–7.46 (m, 2H, Bz-H), 7.58–7.61 (m, 1H, Bz-H), 7.84–7.85 (m, 2H, Ts), 7.95–7.97 (m, 2H, Ts); ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.5, −5.4, 18.2, 21.6, 25.8, 31.6, 59.4, 71.0, 76.6, 77.8, 83.4, 127.9, 128.4, 129.0, 129.7, 130.0, 133.3, 133.5, 145.3, 164.9. Anal. Calcd for $C_{26}H_{36}O_7SSi$: C, 59.97; H, 6.97. Found: C, 60.14; H, 6.83.

3.1.15. {2S-[2-O-tert-Butyldimethylsilyl-ethyl]-3S,4R-epoxy}-tetrahydrofuran (**18**)

Compound **17** (176 mg, 0.34 mmol) and anhydrous K_2CO_3 (224 mg, 1.62 mmol) were dissolved in dry methanol (4 mL), the resulting suspension was stirred for 1.5 h at room temperature. The

mixture was neutralized with acetic acid and evaporated. The residue was purified by silica gel column chromatography (petroleum ether/EtOAc) to yield **18** (74 mg, 89.6%) as a colorless syrup.

$[\alpha]_D^{20}$ −17.10 (*c* 0.025, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.06 (s, 6H, TBDMS-CH_3), 0.90 (s, 9H, TBDMS-^{t}Bu), 1.56–1.61 (m, 1H, 6a-H), 1.64–1.71 (m, 1H, 6b-H), 3.69–3.76 (m, 5H, 7-H, 3-H, 4-H, 5b-H), 3.98 (d, $J_{5a,5b}$=11.0 Hz, 1H, 5a-H), 4.23 (dd, $J_{2,6a}$=5.5 Hz, $J_{2,6b}$=7.5 Hz, 1H, 2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.4, 18.2, 25.9, 34.0, 55.9, 59.1, 59.3, 66.0, 75.2. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.69; H, 9.76.

3.1.16. *{2S-[2-O-tert-Butyldimethylsilyl-ethyl]-3R-hydroxy-4S-(adenin-9-yl)}-tetrahydrofuran (**19b**) and {2S-[2-O-tert-butyldimethylsilyl-ethyl]-3R-(adenin-9-yl)-4S-hydroxy}-tetrahydrofuran (**20b**)*

To a solution of **18** (121 mg, 0.50 mmol) and dry adenine (130 mg, 0.96 mmol) in dry DMF (12 mL), DBU (0.25 mL, 1.64 mmol) was added, the mixture was heated to 110 °C for 5 days. After the mixture was cooled to room temperature, the solvent was evaporated and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH) to give **19b** (white solid, 88 mg, 46.8%) and **20b** (white solid, 9.4 mg, 5.0%).

*Compound **19b***. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.03 (s, 3H, TBDMS-CH_3), 0.04 (s, 3H, TBDMS-CH_3), 0.87 (s, 9H, TBDMS-^{t}Bu), 1.69–1.76 (m, 1H, 6-H), 1.82–1.88 (m, 1H, 6-H), 3.67–3.77 (m, 3H, 2-H, 7-H), 4.10–4.17 (m, 2H, 5-H), 4.28–4.30 (m, 1H, 3-H), 4.83–4.87 (m, 1H, 4-H), 5.72 (d, *J*=6.0 Hz, 1H, 3-OH), 7.23 (br s, 2H, 6-NH_2 in adenine), 8.14 (s, 1H, 2-H in adenine), 8.15 (s, 1H, 8-H in adenine); ^{13}C NMR (125 MHz, DMSO-d_6): δ −5.4, −5.3, 17.9, 25.8, 36.0, 59.5, 61.9, 68.7, 78.8, 80.5, 119.0, 139.2, 149.4, 152.3, 156.0; ESI-TOF MS *m*/*z*: 380.28 $(M+H)^+$, 402.27 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{29}N_5O_3Si$: C, 53.80; H, 7.70; N, 18.45. Found: C, 53.93; H, 7.77; N, 18.35.

*Compound **20b***. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.01 (s, 3H, TBDMS-CH_3), 0.00 (s, 3H, TBDMS-CH_3), 0.86 (s, 9H, TBDMS-^{t}Bu), 1.16–1.22 (m, 2H, 6-H), 3.55–3.59 (m, 3H, 2-H, 7-H), 4.28–4.29 (m, 1H, 5a-H), 4.56–4.58 (m, 2H, 5b-H, 4-H), 4.89 (d, 1H, *J*=4.0 Hz, 3-H), 5.90 (d, 1H, *J*=3.5 Hz, 4-OH), 7.37 (s, 2H, –NH_2 in adenine), 7.96 (s, 1H, 2-H in adenine), 8.23 (s, 1H, 8-H in adenine); ESI-TOF MS *m*/*z*: 380.28 $(M+H)^+$, 402.27 $(M+Na)^+$.

3.1.17. *{2S-[2-O-tert-Butyldimethylsilyl-ethyl]-3R-hydroxy-4S-(thymin-9-yl)}-tetrahydrofuran (**19a**) and {2S-[2-O-tert-butyldimethylsilyl-ethyl]-3R-(thymin-1-yl)-4S-hydroxy}-tetrahydrofuran (**20a**)*

Compounds **19a** (white solid, 35.5%) and **20a** (white solid, 4.0%) were obtained by the same method as that for compounds **19b** and **20b**.

*Compound **19a***. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.03 (s, 3H, TBDMS-CH_3), 0.04 (s, 3H, TBDMS-CH_3), 0.87 (s, 9H, TBDMS-^{t}Bu), 1.69–1.76 (m, 1H, 6-H), 1.82–1.88 (m, 1H, 6-H), 1.92 (s, 3H, thymine-CH_3), 3.67–3.77 (m, 3H, 2-H, 7-H), 4.10–4.17 (m, 2H, 5-H), 4.29–4.31 (m, 1H, 3-H), 4.83–4.86 (m, 1H, 4-H), 5.72 (d, *J*=6.0 Hz, 1H, 3-OH), 7.27 (s, 1H, 6-H in thymine), 9.39 (br s, 1H, 3-NH in thymine); ESI-TOF MS *m*/*z*: 371 $(M+H)^+$. Anal. Calcd for $C_{17}H_{30}N_2O_5Si$: C, 55.11; H, 8.16; N, 7.56. Found: C, 55.16; H, 8.18; N, 7.46.

*Compound **20a***. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.00 (s, 3H, TBDMS-CH_3), 0.01 (s, 3H, TBDMS-CH_3), 0.85 (s, 9H, TBDMS-^{t}Bu), 1.17–1.23 (m, 2H, 6-H), 1.92 (s, 3H, thymine-CH_3), 3.56–3.60 (m, 3H, 2-H, 7-H), 4.28–4.30 (m, 1H, 5a-H), 4.56–4.58 (m, 2H, 5b-H, 4-H), 4.89 (d, 1H, 3-H), 5.90 (d, 1H, 4-OH), 7.27 (s, 1H, 6-H in thymine), 9.39 (br s, 1H, –NH); ESI-TOF MS *m*/*z*: 371 $(M+H)^+$.

3.1.18. *Deprotection procedure of **19a** or **19b** to synthesize **2a** or **2b***

A solution of compound **19b** (56 mg, 0.148 mmol) and TBAF (1 M in THF, 0.3 mL, 0.3 mmol) in THF (2 mL) was stirred for 3 h at room temperature. The resulting mixture was evaporated and the residue was purified by silica gel column chromatography (CH_2Cl_2/MeOH) to give **2b** (26 mg, 66.5%) as a white solid.

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