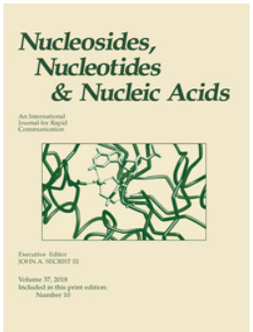

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of 1,1,2-trisubstituted cyclopropane nucleosides in enantiomerically pure forms

Daichi Fushihara[a,c], Hayato Fukuda[a], Hiroshi Abe[c], and Satoshi Shuto[a,b]

[a]Faculty of Pharmaceutical Sciences, Center for Research and Education on Drug Discovery, Hokkaido University, Sapporo, Japan; [b]Center for Research and Education on Drug Discovery, Hokkaido University, Sapporo, Japan; [c]Graduate School of Sciences, Nagoya University, Nagoya, Japan

ABSTRACT

Due to the unique rigid and small steric feature of cyclopropane, cyclopropane nucleosides (CPNs) in which the ribose (deoxyribose) of nucleosides are replaced by a hydroxy-substituted cyclopropane, are of great biological interest. Novel 1,1,2-trisubstituted cyclopropane nucleosides were synthesized in enantiomerically pure forms as potential antiviral agents. In the synthesis, two cyclopropane tosylates, which were prepared from chiral cyclopropane lactones previously reported by us, were used effectively as common intermediates for the CPNs. These CPNs are also potentially useful as nucleoside units to incorporate into oligonucleotides in nucleic acids chemotherapy studies.

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Introduction

Carbocyclic nucleosides can be bioisosteres of natural nucleosides lacking the biologically unstable *N*-ribosyl linkage, and therefore they have been studied due to the biological and pharmacological interest.[1] A number of antiviral and antitumor carbocyclic nucleosides have been reported, typically exemplified by clinically useful entecavir[2] and abacavir[3] (Figure 1). In the course of these studies on carbocyclic nucleosides, we have also studied design and synthesis of anti-RNA virus carbocyclic nucleosides such as **1** derived from neplanocin A, an antibiotic cyclopentene nucleoside, as a prototype.[4]

Because the smallest carbocycle cyclopropane has a characteristic sterically unhindered and rigid structural feature, it is very effective for designing conformationally restricted analogs using various conformationally flexible bioactive prototype compounds.[5] Thus, we have been engaged in medicinal chemistry studies using cyclopropane as a key unit for conformational restriction and identified various pharmacologically active compounds.[6]

CONTACT Satoshi Shuto shu@pharm.hokudai.ac.jp
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Due to the unique feature of cyclopropane, cyclopropane nucleosides

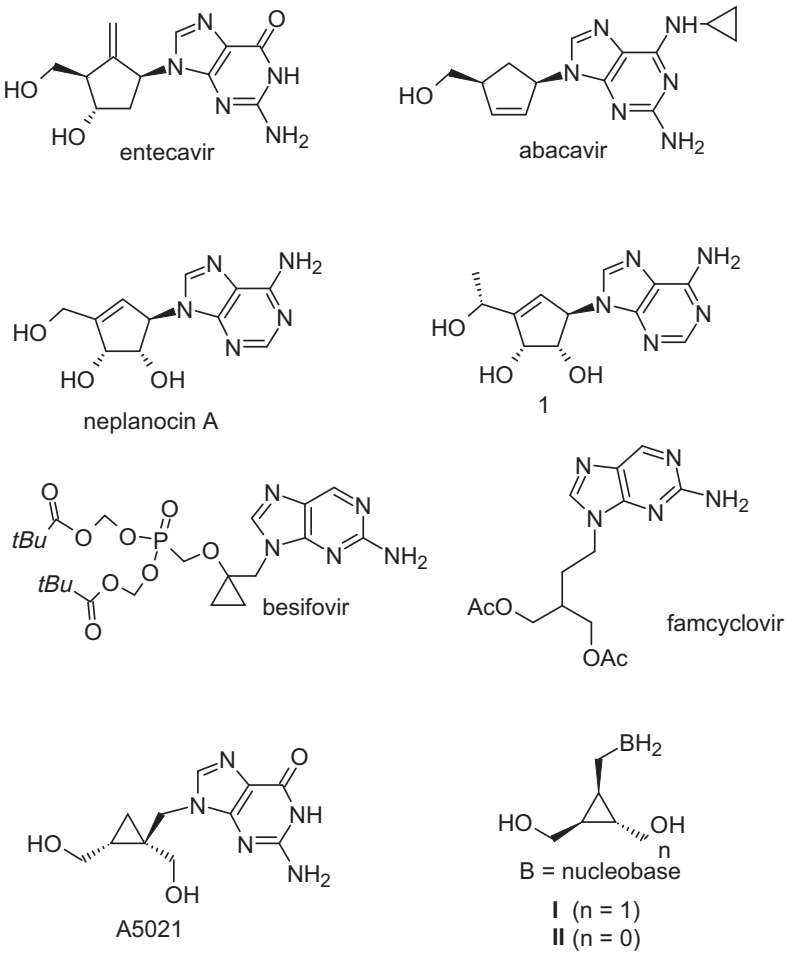


Figure 1. Representative biologically active carbocyclic nucleosides.

(CPNs) are of great interest.[7] Besifovir,[7d] a cyclopropane nucleoside phosphate derivative, was most recently approved as an anti-hepatitis B viral drug, and some other cyclopropane nucleosides also have potent antiviral activity.[7] We recently reported synthesis of chiral 1,2,3-trisubstituted CPNs **I** and **II** using Pd-catalyzed substitution via directing group-mediated C(sp^3)–H activation of a chiral cyclopropane as a key step.[8]

In this paper, we describe cyclopropane nucleosides CPNs **III** and **IV** in enantiomerically pure form[9] as potential antiviral agents (Figure 2). These have regioisomeric structures of A5021 with remarkable anti-herpes virus effects.[7b] CPNs **III** and **IV** are also of interest because they correspond to conformationally restricted analogs of the potent anti-herpes virus drug famcyclovir.[10] Furthermore, these CPNs would be useful as nucleoside

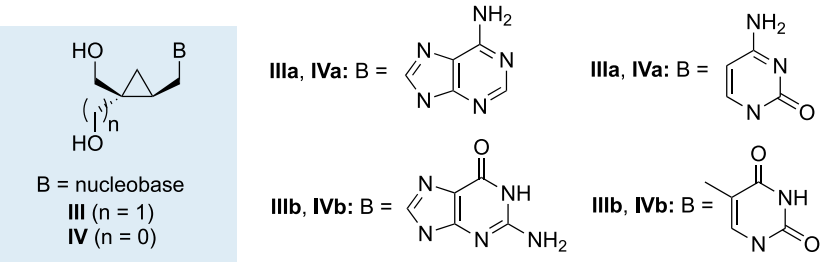


Figure 2. Novel optically active cyclopropane nucleosides **IIIa–d** and **IVa–d**.

units to be incorporated into antisense, siRNA, and aptamer oligonucleotides in nucleic acids chemotherapy studies.

Results and discussion

As described above, we have been engaged in medicinal chemistry studies using cyclopropane as a key structure for conformational restriction of compounds and identified a number of pharmacologically active compounds.[5,6] In these studies, we also have developed various methods for the synthesis of optically active cyclopropane compounds[11,12] which effectively applied to this CPN synthesis. The retrosynthetic analysis is summarized in Figure 3. All of four natural nucleobases in **IIIa–d** and **IVa–d** would be introduced *via* S_N2 substitution reaction using key common intermediates that were cyclopropane tosylates **2** for **IIIa–d** and **4** for **IVa–d**, at a late stage in the synthesis. The tosylate **2** would be prepared from a known chiral tri-substituted cyclopropane lactone **3**.[7b] Another tosylate **4** would be prepared from a chiral methylene cyclopropane **5**. We recently reported a synthesis of **5** from another chiral tri-substituted lactone **6**.[10d] Both of lactones **3** and **6** in high optical purity were readily prepared from (*R*)-epichlorohydrin.[7b,11]

Synthesis of the common intermediate tosylate **2** is shown in Scheme 1. The known chiral lactone **3** prepared from (*R*)-epichlorohydrin[7b] was

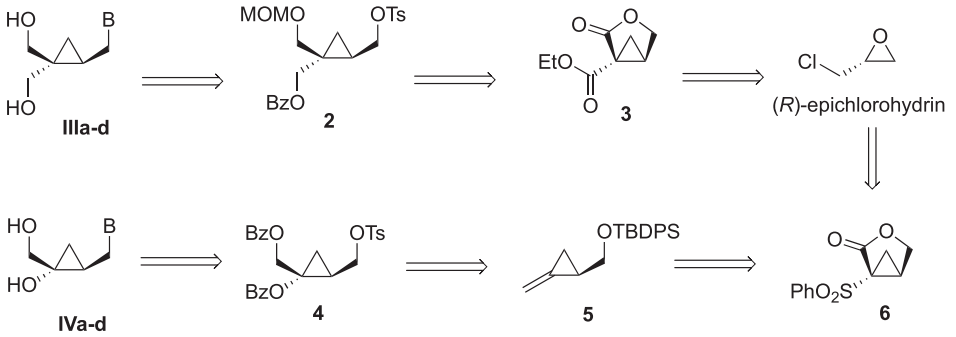
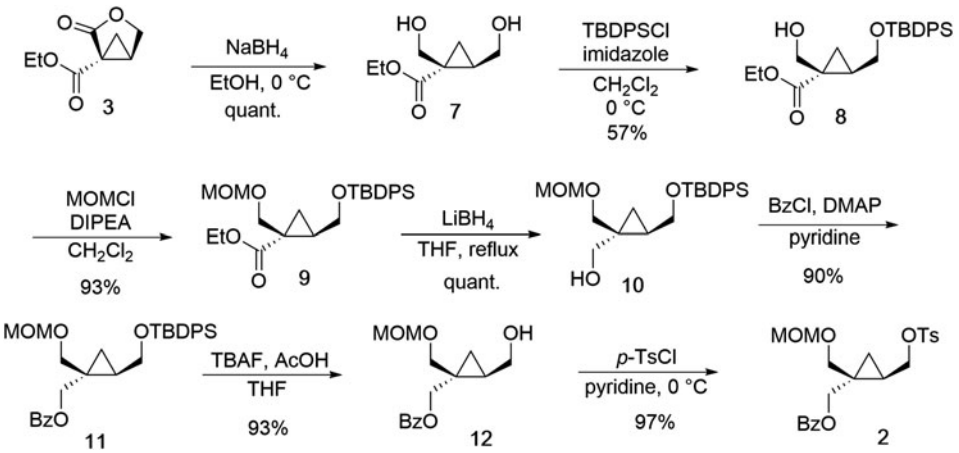


Figure 3. Retrosynthetic analysis for CPNs **III** and **IV**.



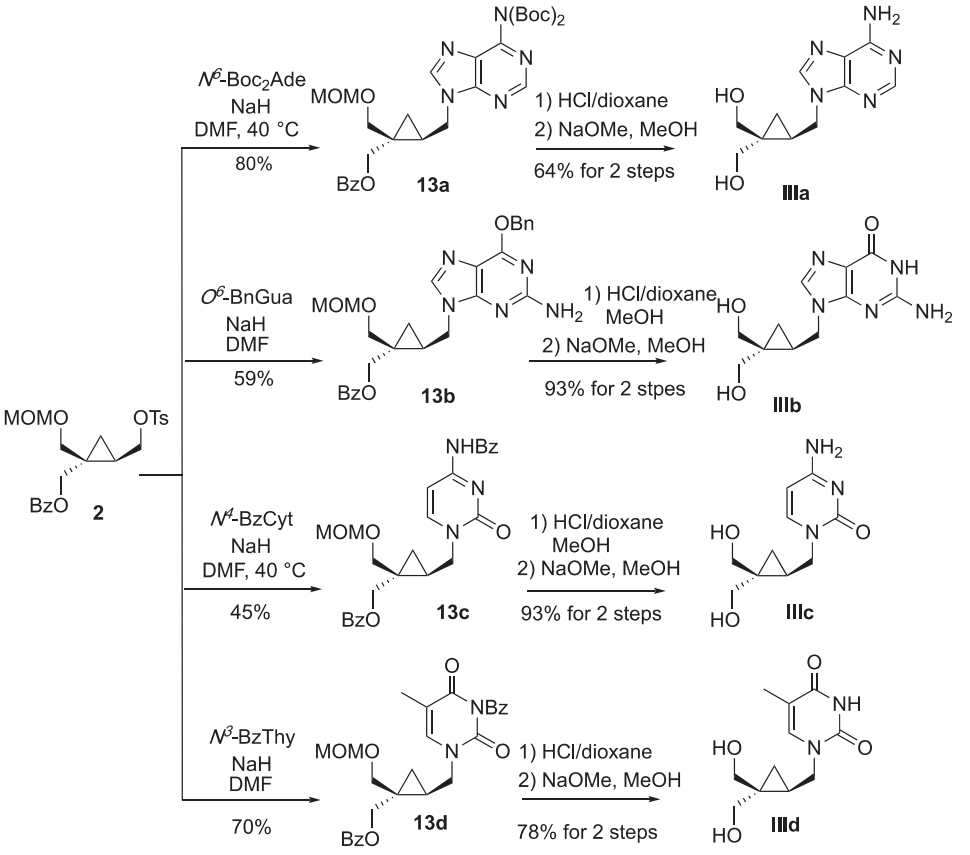
Scheme 1. Synthesis of key common intermediate **2**.

treated with $NaBH_4$ formed diol **7**[7b] of which protecting groups manipulation provided **9**.[11e,f] Reduction of **9** with $LiBH_4$ gave alcohol **10**.[11f] Protecting groups of **10** was again manipulated to afford trihydroxymethylcyclopropane **12**, in which three of the two hydroxyls were protected with a MOM group and a benzoyl group, respectively. Tosylation of the unprotected hydroxyl of **12** gave the common intermediate tosylate **2**.

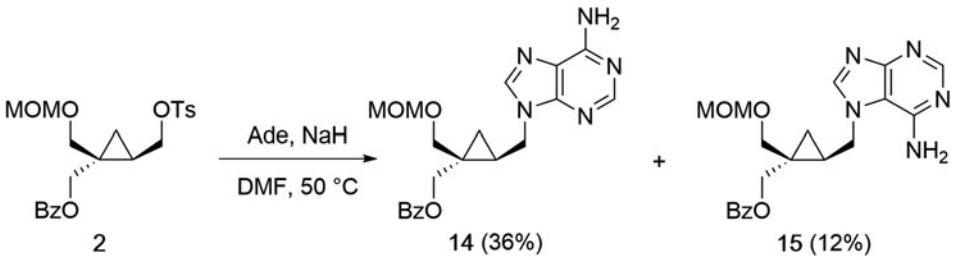
The desired four CPNs **IIIa–d** were successfully synthesized from the tosylate **2** as summarized in Scheme 2. We firstly treated **2** with unprotected adenine and NaH in DMF to give a mixture of the desired N^9-product **14** and the corresponding N^7-regioisoer **15**[13] as shown in Scheme 3. However, when *N*,*N*-di-Boc-adenine (N^6-Boc_2Ade) instead of adenine was used as a nucleophile[14] the N^9-product **13a** was selectively obtained in 80% yield (Scheme 2). Treatment of **2** with O^6-BnGua and NaH in DMF gave mainly the desired N^9-product **13b** in 59% yield (Scheme 2) concomitant with the N^7-isomer **16** (Figure 4).[13] Similar treatments of **2** with N^4-BzCyt or N^3-BzThy in the presence of NaH in DMF successfully provided the corresponding nucleoside products **13c** and **13d**, respectively. Removal of all of the *N*- and/or *O*-protecting groups of **13a–d** were carried out by treating successively with HCl in dioxane or in dioxane/MeOH and with NaOMe/MeOH to furnish the target CPNs **IIIa**, **IIIb**, **IIIc**, and **IIId**, respectively.

Preparation of tosylate **4**, the common intermediate for the synthesis of CPNs **IVa–d**, is shown in Schemes 4 and 5. Oxidation of the optically active methylenecyclopropane **5**[11d] with OsO_4 stereoselectively occurred to afford diol **17** in 92% yield. The stereochemistry of **17** was confirmed by NOE experiments as shown in Figure 5.

After protecting the two hydroxyls of **17** with isopropylidene group, removal of TBDPS group of the resulting acetonide **18** gave **19**. Tosylation



Scheme 2. Synthesis of CPNs **IIIa**, **IIIb**, **IIIc**, and **IIId**.



Scheme 3. Formation of undesired N^7-regioisomers.

of the hydroxyl of **19** was examined under various conditions, however, the desired tosylate **20** was not obtained at all. Introduction of thymine base into **19** under Mitsunobu conditions, which was very effective for our recent synthesis of CPN **I** and **II**, was also unsuccessful. Thus, we speculated that, when an electron-withdrawing tosyl group was introduced, the cyclopropane ring-opening readily occurred due to the electron-donating effect of a lone pair of the oxygen directly attached to the cyclopropane ring as indicated in Scheme 4.[15] Therefore, we introduced an electron-

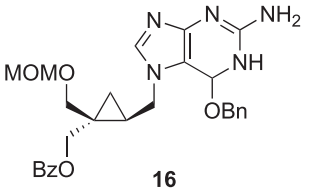
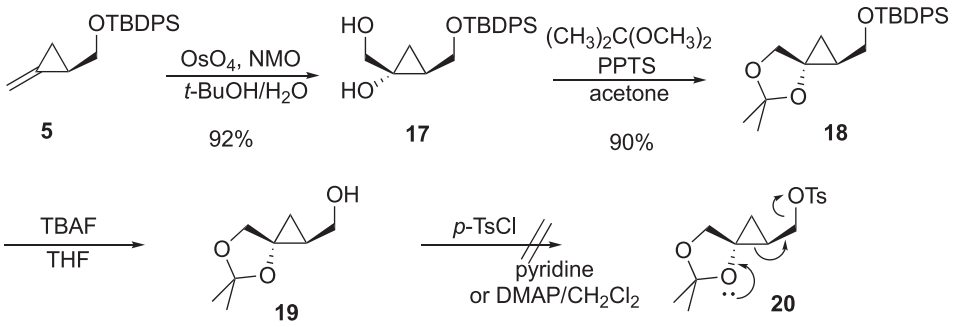


Figure 4. Structure of the N^7-regioisomer **16**.



Scheme 4. Attempt to synthesize tosylate **20**.

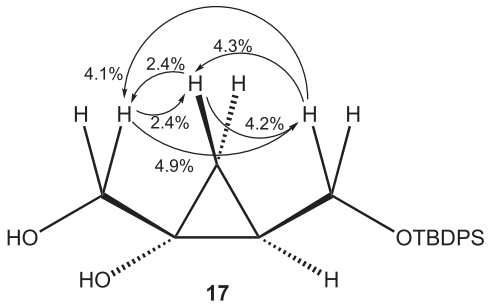
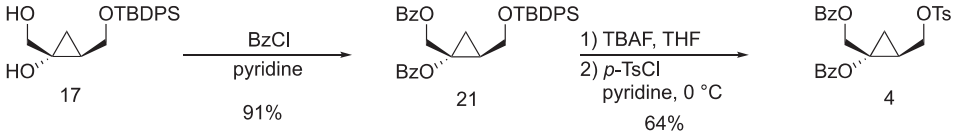


Figure 5. NOE data of the osmium oxidation product **17**.

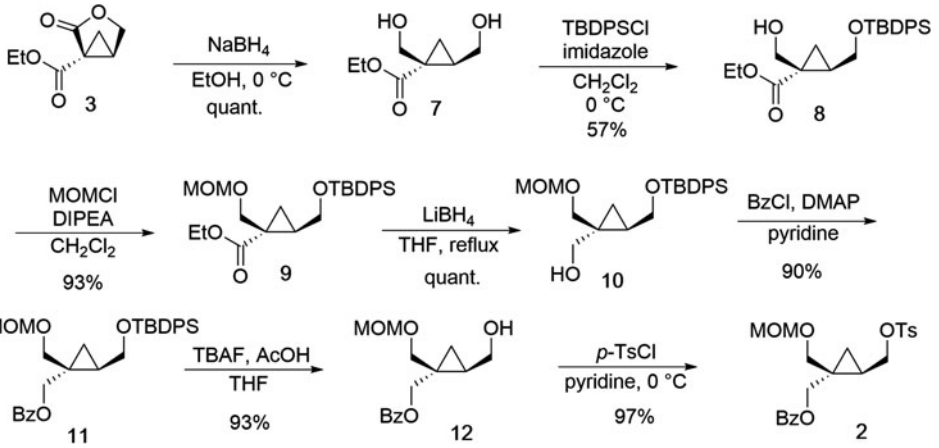
withdrawing benzoyl group at the hydroxyl to prevent the cyclopropane ring-opening. Treatment of **17** with BzCl/pyridine gave dibenzoate **21**, of which treatment with TBAF/THF followed by with TsCl/pyridine provided the desired tosylate **4** in a pure form after silica gel column chromatography (Scheme 5).

The key intermediate tosylate **4** in hand, we investigated the synthesis of CPNs **IVa–d** (Scheme 6). By the procedure same to the synthesis of CPNs **IIIa–d** described above, CPNs **IVa**, **IVb**, and **IVd** were successfully obtained. However, during deprotection procedure of guanine derivative **22b**, it unfortunately decomposed, and thus we could not obtain **IVb**. Due to the electron-withdrawing property of guanine base, ring opening of the cyclopropane ring of **IVb** might occur like the case of tosylate **20**.

As described, we successfully synthesized CPNs **IIIa**, **IIIb**, **IIIc** and **IIId**, CPNs **IIVa**, **IVb** and **IVd** in enantiomerically pure forms.



Scheme 5. Synthesis of tosylate **4**.



Scheme 6. Synthesis of CPNs **IVa**, **IVc**, and **IVd**.

Experimental section

General information. All commercially available materials were used as received unless otherwise noted. Column chromatography was performed using silica gel Wakogel® 60 N (spherical, neutral, 63–210 μm) (Wako) and Chromatorex NH DM1020 (Fuji Silysia). Compounds were characterized by ^{1}H NMR, 13C NMR, and mass spectra. Nuclear magnetic resonance spectra were recorded on a JEOL 400 or 500 MHz instruments. ^{1}H NMR spectra are reported in δ units and parts per million (ppm) and were measured relative to signals for tetramethylsilane (0.00 ppm) in the deuterated solvent. 13C NMR spectra are reported in ppm relative to $CDCl_3$ (77.00 ppm) unless otherwise stated, and were obtained with ^{1}H decoupling. Low- and high-resolution mass analysis was performed on a double-focusing high-resolution magnetic sector mass-analyzer instrument.

(1*R*,2*R*)-[1-Benzoyloxymethyl-2-(*t*-butyldiphenylsilyloxy)methyl-1-(methoxymeth-yloxy)methyl]cyclopropane (11). To a solution of **10**[11f] (755 mg, 1.82 mmol) in pyridine (9.1 mL) were added DMAP (11.3 mg, 92.5 μmol) and benzoyl chloride (525 mg, 4.55 mmol) at room temperature. After stirring the mixture at room temperature for 3.5 h, the reaction was quenched with cold water and evaporated in vacuo. The residue was partitioned between AcOEt and saturated aqueous $NaHCO_3$. The organic layer was washed with aqueous HCl (1 M) and brine, dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by

silica gel column chromatography (20% AcOEt in hexane) to give **11** (850 mg, 1.64 mmol, 90%) as a colorless oil. [α]18D : −3.01 ($c = 3.75$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, $J = 8.0$ Hz, 2 H, aromatic), 7.63–7.72 (m, 4 H, aromatic), 7.52–7.54 (m, 1 H, aromatic), 7.32–7.45 (m, 8 H, aromatic), 4.60 (s, 2 H, –O$\underline{CH_2}$O–), 4.36 (d, $J = 11.4$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.15 (d, $J = 11.4$ Hz, 1 H, BzO$\underline{CH_2}$C–), 3.73–3.87 (m, 2 H, MOMO$\underline{CH_2}$C–, –CH$\underline{CH_2}$O–), 3.66–3.71 (m, 1 H, –CH$\underline{CH_2}$O–), 3.58 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.28 (s, 3 H, $\underline{CH_3}$O–), 1.36 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 1.03 (s, 9 H, –*t*Bu), 0.84 (m, 1 H, –C$\underline{CH_2}$CH–), 0.55 (m, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 100 MHz) δ 162.3, 135.5, 133.6, 133.6, 132.8, 130.5, 130.1, 129.6, 128.3, 127.6, 127.6, 96.2, 69.1, 67.2, 63.4, 55.1, 26.7, 24.2, 24.1, 19.1, 13.7; HRMS (ESI) calcd for $C_{31}H_{38}O_5NaSi$: 541.23807, found for 541.23836 [$(M + Na)^+$].

(1*R*,2*R*)-[1-Benzoyloxymethyl-2-hydroxymethyl-1-(methoxymethyloxy)-methyl]-cyclopropane (12). To a solution of **11** (79.8 mg, 154 μmol) in THF (1.5 mL) were added AcOH (13 mL, 231 μmol) and a solution of tetrabutylammonium fluoride (1 M solution in THF, 0.23 mL, 231 μmol) at room temperature. After stirring the mixture at room temperature for 6 h, the solvent was evaporated in vacuo. The residue was partitioned between AcOEt and saturated aqueous NH_4Cl. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (33–50% AcOEt in hexane) to give **12** (40.2 mg, 143 μmol, 93%) as a colorless oil. [α]19D : −2.69 ($c = 4.00$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, $J = 8.0$ Hz, 2 H, aromatic), 7.57 (t, $J = 8.0$ Hz, 1 H, aromatic), 7.45 (dd, $J = 8.0$, 8.0 Hz, 2 H, aromatic), 4.67 (s, 2 H, –O$\underline{CH_2}$O–), 4.62 (d, $J = 12.0$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.12 (d, $J = 12.0$ Hz, 1 H, BzO$\underline{CH_2}$C–), 3.96–4.02 (m, 2 H, MOMO$\underline{CH_2}$C–, –CH$\underline{CH_2}$O–), 3.30–3.42 (m, 5 H, MOMO$\underline{CH_2}$C–, –CH$\underline{CH_2}$O–, $\underline{CH_3}$O–), 1.46 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 0.98 (dd, $J = 8.0$, 6.0 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.55 (dd, $J = 6.0$, 4.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 100 MHz) δ 166.4, 132.9, 130.1, 129.5, 128.3, 96.5, 69.0, 68.3, 62.5, 55.5, 24.3, 24.0, 14.2; HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$: 303.12029, found for 303.12040 [$(M + Na)^+$].

(1*R*,2*R*)-[1-Benzoyloxymethyl-1-(methoxymethyloxy)methyl-2-(tosyloxy)methyl]-cyclopropane (2). To a solution of **12** (261 mg, 931 μmol) in pyridine (4.7 mL) was added TsCl (799 mg, 4.19 mmol) at 0 °C. After stirring the mixture at 0 °C for 5.5 h, the reaction mixture was partitioned between AcOEt and aqueous HCl (1 M). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (20% AcOEt in hexane) to give **2** (392 mg, 902 μmol, 97%) as a colorless oil. [α]19D : −3.67 ($c = 3.21$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, $J = 8.0$ Hz, 2 H, aromatic), 7.79 (d, $J = 8.4$ Hz, 2 H,

aromatic), 7.57 (t, $J = 8.0$ Hz, 1 H, aromatic), 7.45 (dd, $J = 8.0$, 8.0 Hz, 2 H, aromatic), 7.32 (d, $J = 8.4$ Hz, 2 H, aromatic), 4.58 (m, 2 H, –O$\underline{CH_2}$O–), 4.26 (d, $J = 11.6$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.13–4.21 (m, 3 H, –CH$\underline{CH_2}$O–, BzO$\underline{CH_2}$C–), 3.69 (d, $J = 11.2$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.48 (d, $J = 11.2$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.31 (s, 3 H, $\underline{CH_3}$O–), 2.43 (s, 3 H, $\underline{CH_3}$Ph–), 1.36 (m, 1 H, –C$\underline{CH}$($\underline{CH_2}$)$\underline{CH_2}$–), 0.99 (dd, $J = 8.8$, 5.8 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.55 (dd, $J = 5.8$, 5.6 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 100 MHz) δ 166.3, 144.7, 133.3, 133.0, 130.0, 129.8, 129.5, 128.4, 127.8, 96.3, 70.6, 68.1, 66.9, 55.3, 25.2, 21.6, 20.0, 14.3; HRMS (ESI) calcd for $C_{22}H_{26}O_7NaS$: 457.12914, found for 457.12915 [$(M + Na)^+$].

(1*R*,2*R*)-{1-Benzoyloxymethyl-2-(adenin-9-yl)methyl-1-(methoxymethyloxy)-methyl}cyclopropane (14) and (1*R*,2*R*)-{1-benzoyloxymethyl-2-(adenin-7-yl)methyl-1-(methoxymethyloxy)-methyl}cyclopropane (15). To a solution of adenine (9.72 mg, 71.9 μmol) in DMF (0.25 mL) was added NaH (60% dispersion in mineral oil, 2.88 mg, 71.9 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the mixture was added a solution of **2** (28.4 mg, 65.4 μmol) in DMF (0.10 mL) at room temperature. After stirring the mixture at 50 °C for 4 h, the resulting mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (5–9% MeOH in $CHCl_3$) to give **14** (9.33 mg, 23.5 μmol, 36%) as a colorless waxy solid and **15** (3.12 mg, 7.83 μmol, 12%) as a colorless waxy solid. **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H, adenine-H2), 8.07 (s, 1 H, adenine-H8), 7.96 (d, $J = 8.0$ Hz, 2 H, aromatic), 7.56 (t, $J = 7.7$ Hz, 1 H, aromatic), 7.44 (dd, $J = 8.0$, 7.7 Hz, 2 H, aromatic), 5.82 (s, 2 H, NH_2–), 4.64 (s, 2 H, –O$\underline{CH_2}$O–), 4.38–4.44 (m, 2 H, –CH$\underline{CH_2}$N–, BzO$\underline{CH_2}$C–), 4.26 (dd, $J = 14.8$, 8.0 Hz, 1 H, –CH$\underline{CH_2}$N–), 4.19 (d, $J = 11.6$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.02 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.60 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.33 (s, 3 H, $\underline{CH_3}$O–), 1.61 (m, 1 H, –C$\underline{CH}$($\underline{CH_2}$)$\underline{CH_2}$–), 1.07 (dd, $J = 9.0$, 5.9 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.79 (dd, $J = 5.9$, 5.6 Hz, 1 H, –C$\underline{CH_2}$CH–); UV (water) λ_{max} 261 nm. **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1 H, adenine-H2), 8.14 (s, 1 H, adenine-H8), 7.99 (d, $J = 8.4$ Hz, 2 H, aromatic), 7.69 (t, $J = 8.0$ Hz, 1 H, aromatic), 7.47 (dd, $J = 8.4$, 8.0 Hz, 2 H, aromatic), 5.40 (s, 2 H, NH_2–), 4.67 (s, 2 H, –O$\underline{CH_2}$O–), 4.58 (dd, $J = 15.2$, 6.5 Hz, 1 H, –CH$\underline{CH_2}$N–), 4.43 (d, $J = 11.8$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.34 (dd, $J = 15.2$, 6.5 Hz, 1 H, –CH$\underline{CH_2}$N–), 4.21 (d, $J = 11.8$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.10 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.54 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.36 (s, 3 H, $\underline{CH_3}$O–), 1.57 (m, 1 H, –C$\underline{CH}$($\underline{CH_2}$)$\underline{CH_2}$–), 1.16 (dd, $J = 9.0$, 5.8 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.82 (dd, $J = 6.0$, 5.6 Hz, 1 H, –C$\underline{CH_2}$CH–); UV (water) λ_{max} 265 nm.

(1*R*,2*R*)-{1-Benzoyloxymethyl-2-[*N*6,N^6-bis(*t*-butoxycarbonyl)adenin-9-yl)methyl-1-(methoxymethyloxy)methyl]cyclopropane (13a). To a solution of *N*,*N*-di-Boc-adenine[16] (180 mg, 506 μmol) in DMF (2.3 mL) was added NaH (60% dispersion in mineral oil, 20.2 mg, 506 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the mixture was added a solution of **2** (200 mg, 460 μmol) in DMF (2.3 mL) at room temperature. After stirring the mixture at 40 °C for 24 h, the resulting mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (33% AcOEt in hexane) to give **13a** (221 mg, 369 μmol, 80%) as a white solid. [α]17D : 2.98 ($c = 0.62$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (s, 1 H, adenine-H2), 8.44 (s, 1 H, adenine-H8), 8.01 (d, $J = 7.5$ Hz, 2 H, aromatic), 7.57 (d, $J = 7.4$ Hz, 1 H, aromatic), 7.45 (dd, $J = 7.5$, 7.4 Hz, 2 H, aromatic), 4.61 (m, 2 H, –O$\underline{CH_2}$O–), 4.53 (dd, $J = 14.7$, 7.0 Hz, 1 H, –CH$\underline{CH_2}$N–), 4.45 (d, $J = 11.5$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.37 (dd, $J = 14.7$, 8.0 Hz, 1 H, –CH$\underline{CH_2}$N–), 4.18 (d, $J = 11.5$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.09 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.58 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.31 (s, 3 H, $\underline{CH_3}$O–), 1.65 (m, 1 H, –C$\underline{CH}(CH_2)CH_2$–), 1.45 (s, 18 H, –*t*Bu), 1.10 (dd, $J = 8.8$, 5.7 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.55 (dd, $J = 5.7$, 5.5 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 166.0, 153.1, 151.5, 150.1, 149.8, 144.7, 132.8, 129.6, 129.2, 128.3, 128.1, 96.1, 83.2, 68.0, 66.9, 55.0, 42.9, 27.4, 25.1, 20.8, 14.0; HRMS (ESI) calcd for $C_{30}H_{39}O_8N_5Na$: 620.26908, found for 620.26986 [$(M + Na)^+$].

(1*R*,2*R*)-[1-Benzoyloxymethyl-2-(O^6-benzylguanin-9-yl)methyl-1-(methoxymethyl-oxy)methyl]cyclopropane (13b), (1*R*,2*R*)-[1-benzoyloxymethyl-2-(O^6-benzylguanin-7-yl)methyl-1-(methoxymethyloxy)methyl]cyclopropane (16). To a solution of O^6-benzylguanine (36.7 mg, 152 μmol) in DMF (0.55 mL) was added NaH (60% dispersion in mineral oil, 6.08 mg, 152 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the mixture was added a solution of **2** (60 mg, 138 μmol) in DMF (0.14 mL) at room temperature. After stirring the mixture at room temperature for 5 h, the reaction mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (5% MeOH in $CHCl_3$) to give **13b** (38.9 mg, 77.3 μmol, 56%) as a white solid and **16** (26.4 mg, 52.4 μmol, 38%) as a white solid. **13b**: [α]17D : 7.43 ($c = 1.09$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.96 (d, $J = 7.0$ Hz, 2 H, aromatic), 7.84 (s, 1 H, guanine-H8), 7.31–7.56 (m, 8 H, aromatic), 5.57 (s, 2 H, –O$\underline{CH_2}$Ph), 4.84 (s, 2 H, –NH_2), 4.65 (m, 2 H, –O$\underline{CH_2}$O–), 4.35 (d, $J = 11.6$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.11–4.27

(m, 3 H, BzO$\underline{CH_2}$C–, –CH$\underline{CH_2}$N–), 3.99 (d, $J = 11.2$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.61 (d, $J = 11.2$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.34 (s, 3 H, $\underline{CH_3}$O–), 1.57 (m, 1 H, –C$\underline{CH}(CH_2)CH_2$–), 1.05 (dd, $J = 9.2$, 5.8 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.75 (dd, $J = 6.0$, 5.8 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 166.3, 164.0, 159.1, 157.0, 144.6, 136.0, 133.1, 129.8, 129.4, 128.6, 128.4, 128.4, 128.3, 107.1, 96.4, 68.3, 68.1, 67.1, 55.4, 46.7, 25.2, 22.0, 14.1; HRMS (ESI) calcd for $C_{27}H_{30}O_5N_5$: 504.22415, found for 504.22405 $[(M+H)^+]$; UV (water) λ_{max} 281 nm. **16**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93–7.96 (m, 3 H, guanine-H8, aromatic), 7.57 (t, $J = 7.6$ Hz, 1 H, aromatic), 7.33–7.47 (m, 7 H, aromatic), 5.52 (s, 2 H, –O$\underline{CH_2}$Ph), 4.93 (s, 2 H, –NH_2), 4.56 (m, 2 H, –O$\underline{CH_2}$O–), 4.24–4.39 (m, 3 H, BzO$\underline{CH_2}$C–, –CH$\underline{CH_2}$N–), 4.08 (d, $J = 12.0$ Hz, 1 H, BzO$\underline{CH_2}$C–), 3.87 (d, $J = 10.8$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.37 (d, $J = 10.8$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.29 (s, 3 H, $\underline{CH_3}$O–), 1.54 (m, 1 H, –C$\underline{CH}(CH_2)CH_2$–), 0.91 (dd, $J = 9.2$, 5.6 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.66 (dd, $J = 5.6$, 5.6 Hz, 1 H, –C$\underline{CH_2}$CH–); UV (water) λ_{max} 295 nm.

(1*R*,2*R*)-[2-(N^4-Benzoylcytosin-1-yl)methyl-1-benzoyloxymehtyl-1-(methoxymeth-yloxy)methyl]cyclopropane (13c). To a solution of N^4-benzoylcytosine (109 mg, 506 μmol) in DMF (2.3 mL) was added NaH (60% dispersion in mineral oil, 20.2 mg, 506 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the mixture was added a solution of **2** (200 mg, 460 μmol) in DMF (2.3 mL) at room temperature. After stirring the mixture at 40 °C for 24 h, the reaction mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (1% MeOH in $CHCl_3$) to give **13c** (99.7 mg, 208 μmol, 45%) as a white solid. [α]24D : 12.35 ($c = 4.73$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (br, 1 H, –NH), 8.01–8.04 (m, 3 H, aromatic, cytosine-H6), 7.92 (d, $J = 7.5$ Hz, 2 H, aromatic), 7.53–7.62 (m, 2 H, aromatic), 7.43–7.52 (m, 5 H, aromatic, cytosine-H5), 4.63 (m, 2 H, –O$\underline{CH_2}$O–), 4.36 (d, $J = 11.3$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.22–4.27 (m, 2 H, BzO$\underline{CH_2}$C–, –CH$\underline{CH_2}$N–), 3.91–3.98 (m, 2 H, MOMO$\underline{CH_2}$C–, –CH$\underline{CH_2}$N–), 3.56 (d, $J = 11.0$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.32 (s, 3 H, $\underline{CH_3}$O–), 1.54 (m, 1 H, –C$\underline{CH}(CH_2)CH_2$–), 1.06 (dd, $J = 8.5$, 5.3 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.77 (dd, $J = 6.0$, 5.3 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 166.6, 166.2, 161.9, 155.6, 148.3, 133.0, 133.0, 132.9, 129.8, 129.3, 128.8, 128.3, 127.4, 96.4, 68.5, 67.2, 55.3, 48.7, 25.1, 20.4, 14.0; HRMS (ESI) calcd for $C_{26}H_{28}O_6N_3$: 478.19726, found for 478.19737 $[(M+H)^+]$.

{(1*R*,2*R*)-[2-(3-Benzoylthymin-1-yl]methyl-1-benzoyloxymethyl-1-(methoxymeth-yloxy)methyl]cyclopropane (13d). To a solution of N^3-benzoylthymine[17] (159 mg, 690 μmol) in DMF (2.3 mL) was added

NaH (60% dispersion in mineral oil, 27.6 mg, 690 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the mixture was added a solution of **2** (200 mg, 460 μmol) in DMF (2.3 mL) at room temperature. After stirring the mixture at room temperature for 24 h, the reaction mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (50% AcOEt in hexane) to give **13d** (158 mg, 321 μmol, 70%) as a white solid. [α]18D : 14.38 ($c = 0.66$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.03 (d, $J = 7.5$ Hz, 2 H, aromatic), 7.91 (d, $J = 8.5$ Hz, 2 H, aromatic), 7.62 (t, $J = 6.5$ Hz, 1 H, aromatic), 7.55 (t, $J = 7.5$ Hz, 1 H, aromatic), 7.38–7.50 (m, 5 H, aromatic, thymine-H6), 4.61 (s, 2 H, –O$\underline{CH_2}$O–), 4.38 (d, $J = 10.5$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.18 (d, $J = 10.5$ Hz, 1 H, BzO$\underline{CH_2}$C–), 4.01 (dd, $J = 14.4$, 7.0 Hz, 1 H, –CH$\underline{CH_2}$N–), 3.95 (d, $J = 10.8$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.76 (dd, $J = 14.4$, 7.8 Hz, 1 H, –CH$\underline{CH_2}$N–), 3.49 (d, $J = 10.8$ Hz, 1 H, MOMO$\underline{CH_2}$C–), 3.33 (s, 3 H, $\underline{CH_3}$O–), 1.86 (s, 3 H, C^5CH_3), 1.44 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 1.00 (dd, $J = 8.5$, 5.3 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.69 (dd, $J = 5.5$, 5.3 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 169.0, 166.2, 163.0, 149.8, 140.1, 134.9, 133.0, 131.3, 130.1, 130.0, 129.3, 129.0, 128.3, 110.3, 96.3, 68.4, 67.1, 55.2, 46.8, 25.0, 20.8, 13.8, 12.1; HRMS (ESI) calcd for $C_{27}H_{28}O_7N_2Na$: 515.17887, found for 515.17910 [$(M + Na)^+$].

(*R*)-[2-(Adenin-9′-yl)methyl-1,1-bis(hydroxymethyl)]cyclopropane (IIIa). A solution of **13a** (210 mg, 350 μmol) in HCl (4.0 M in dioxane, 3.5 mL) was stirred at room temperature for 6 h, and then the solvent was evaporated in vacuo. To the solution of the residue in MeOH (3.5 mL) was added a solution of NaOMe (5 M in MeOH, 94 μL, 470 μmol) at room temperature. After stirring the mixture at room temperature for 2 h, the reaction was quenched with aqueous HCl (1 M) and evaporated in vacuo. The residue was purified by NH silica gel column chromatography (17% MeOH in $CHCl_3$) to give **IIIa** (56.2 mg, 225 μmol, 64%) as a white solid. mp. 163.1–165.2 °C; [α]24D : −7.40 ($c = 0.25$, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 8.29 (s, 1 H, adenine-H2), 8.20 (s, 1 H, adenine-H8), 4.34 (d, $J = 7.5$ Hz, 2 H, –CH$\underline{CH_2}$N–), 4.02 (d, $J = 11.8$ Hz, 1 H, OH$\underline{CH_2}$C–), 3.62–3.67 (m, 2 H, OH$\underline{CH_2}$C–), 3.39 (d, $J = 11.3$ Hz, 1 H, O$\underline{H}$C$\underline{H_2}$C–), 1.39 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 0.79 (dd, $J = 8.5$, 5.3 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.61 (dd, $J = 5.3$, 5.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR (CD_3OD, 125 MHz) δ 157.3, 153.53, 150.5, 142.8, 120.0, 66.9, 62.4, 44.5, 30.7, 22.2, 13.7; HRMS (ESI) calcd for $C_{11}H_{16}O_2N_5$: 250.12985, found for 250.13010 [$(M + H)^+$].

(*R*)-[2-(Guanin-9-yl)methyl-1,1-bis(hydroxymethyl)]cyclopropane (IIIb). To a solution of **13b** (79.0 mg, 157 μmol) in MeOH (0.78 mL) was added a

solution of HCl (4.0 M in dioxane, 0.78 mL) at room temperature. After stirring the mixture at room temperature for 5 h, the solvent was evaporated in vacuo. To the solution of the residue in MeOH (0.72 mL) was added a solution of NaOMe (5 M in MeOH, 42 µL, 210 µmol) at room temperature. After stirring the mixture at room temperature for 2 h, the reaction mixture was quenched with aqueous HCl (1 M) and evaporated in vacuo. The residue was purified by NH silica gel column chromatography (17% MeOH in $CHCl_3$) to give **IIIb** (38.9 mg, 146 µmol, 93%) as a white solid. mp. 213.2–215.1 °C; [α]23D : −9.42 ($c = 0.19$, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 7.88 (s, 1 H, guanine-H8), 4.19 (dd, $J = 14.7$, 7.5 Hz, 1 H, –CHC$\underline{H_2}$N–), 4.11 (dd, $J = 14.7$, 7.8 Hz, 1 H, –CHC$\underline{H_2}$N–), 3.99 (d, $J = 11.8$ Hz, 1 H, OHC$\underline{H_2}$C–), 3.60–3.64 (m, 2 H, OHC$\underline{H_2}$C–), 3.38 (d, $J = 11.3$ Hz, 1 H, OHC$\underline{H_2}$C–), 1.35 (m, 1 H, –CC$\underline{H}$(CH_2)C$\underline{H_2}$–), 0.76 (dd, $J = 8.8$, 5.4 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.59 (dd, $J = 5.4$, 5.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR (CD_3OD, 125 MHz) δ 159.5, 155.3, 152.9, 139.7, 117.4, 67.0, 62.5, 44.1, 30.6, 22.3, 13.8; LRMS (ESI) *m/z* 266 [$(M + H)^+$]; HRMS (ESI) calcd for $C_{11}H_{16}O_3N_5$: 266.12477, found for 266.12512 [$(M + H)^+$].

(*R*)-[2-(Cytosin-1-yl)methyl-1,1-bis(hydroxymethyl)]cyclopropane (IIIc). To a solution of **13c** (86.9 mg, 181 µmol) in MeOH (0.91 mL) was added a solution of HCl (4.0 M in dioxane, 0.91 mL) at room temperature. After stirring the mixture at room temperature for 5 h, the solvent was evaporated in vacuo. To the solution of the residue in MeOH (1.8 mL) was added a solution of NaOMe (5 M in MeOH, 97 µL, 485 µmol) at room temperature. After stirring the mixture at room temperature for 2 h, the reaction mixture was quenched with aqueous HCl (1 M) and evaporated in vacuo. The residue was purified by NH silica gel column chromatography (17% MeOH in $CHCl_3$) to give **IIIc** (38.3 mg, 170 µmol, 93%) as a white solid. mp. 203.4–205.8 °C; [α]21D : −20.28 ($c = 0.24$, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 7.73 (d, $J = 7.3$ Hz, 1 H, cytosine-H6), 5.86 (d, $J = 7.3$ Hz, 1 H, cytosine-H5), 3.99 (dd, J = 14.3, 7.3 Hz, 1 H, –CHC$\underline{H_2}$N–), 3.94 (d, $J = 11.3$ Hz, 1 H, OHC$\underline{H_2}$C–), 3.80 (dd, J = 14.3, 7.3 Hz, 1 H, –CHC$\underline{H_2}$N–), 3.62 (d, $J = 11.8$ Hz, 1 H, OHC$\underline{H_2}$C–), 3.56 (d, $J = 11.8$ Hz, 1 H, OHC$\underline{H_2}$C–), 3.36 (d, $J = 11.3$ Hz, 1 H, OHC$\underline{H_2}$C–), 1.23 (m, 1 H, –CC$\underline{H}$(CH_2)C$\underline{H_2}$–), 0.72 (dd, $J = 8.8$, 5.2 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.51 (dd, $J = 5.5$, 5.2 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR (CD_3OD, 125 MHz) δ 167.9, 159.3, 147.3, 95.8, 67.1, 62.6, 30.4, 21.8, 13.3; HRMS (ESI) calcd for $C_{10}H_{16}O_3N_3$: 226.11862, found for 226.11885 [$(M + H)^+$].

(*R*)-[2-(Thymin-1-yl)methyl-1,1-bis(hydroxymethyl)]cyclopropane (IIId). A solution of **13d** (146 mg, 296 µmol) in HCl (4.0 M in dioxane, 3.0 mL) was stirred at room temperature for 6 h, and then the solvent was evaporated in vacuo. To the solution of the residue in MeOH (3.0 mL) was added a solution of NaOMe (5 M in MeOH, 0.16 mL, 800 µmol) at room temperature. After

stirring the mixture at room temperature for 2 h, the reaction mixture was quenched with aqueous HCl (1 M) and evaporated in vacuo. The residue was purified by silica gel column chromatography (5–9% MeOH in $CHCl_3$) to give **IIId** (55.3 mg, 230 μmol, 78%) as a white amorphous solid. [α]20D : −17.12 ($c = 2.57$, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.59 (d, $J = 0.8$ Hz, 1 H, thymine-H6), 4.61 (s, 2 H, –O$\underline{CH_2}$O–), 3.763.82 (m, 2 H, OH$\underline{CH_2}$C–, –CH$\underline{CH_2}$N–), 3.79 (dd, $J = 14.5$, 7.5 Hz, 1 H, –CH$\underline{CH_2}$N–), 3.60 (d, $J = 11.3$ Hz, 1 H, OH$\underline{CH_2}$C–), 3.56 (d, $J = 11.8$ Hz, 1 H, OH$\underline{CH_2}$C–), 3.39 (d, $J = 11.3$ Hz, 1 H, OH$\underline{CH_2}$C–), 1.87 (d, $J = 0.8$ Hz, 3 H, tymine-5–CH_3), 1.23 (m, 1 H, –C$\underline{CH}(CH_2)CH_2$–), 0.73 (dd, $J = 8.5$, 5.0 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.53 (dd, $J = 5.5$, 5.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR (CD_3OD, 125 MHz) δ 166.9, 153.1, 143.1, 111.0, 67.1, 62.6, 48.4, 30.3, 21.5, 13.5, 12.2; HRMS (ESI) calcd for $C_{11}H_{16}O_4N_2Na$: 263.10023, found for 263.10022 [$(M + Na)^+$].

(1*R*,2*S*)-[2-(*t*-Butyldiphenylsilyloxy)methyl-1-hydroxy-1-hydroxymethyl]-cyclo-propane (17). To a solution of NMO (24.0 mg, 204 μmol) in acetone (0.23 mL) were added water (0.46 mL) and a solution of OsO_4 (5 mg/mL in *t*BuOH, 23 μL, 0.465 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the mixture was added a solution of **5**[10d] (30.0 mg, 93.0 μmol) in acetone (0.23 mL) at room temperature. After stirring the mixture at room temperature for 50 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and evaporated in vacuo. The residue was partitioned between $CHCl_3$ and water, and the organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by silica gel column chromatography (33% AcOEt in hexane) to give **17** (30.5 mg, 85.5 μmol, 92%) as a colorless oil. [α]19D : 2.51 ($c = 2.40$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65–7.72 (m, 4 H, aromatic), 7.39–7.49 (m, 6 H, aromatic), 4.03–4.09 (m, 2 H, OH$\underline{CH_2}$C–, –CH$\underline{CH_2}$O–), 3.59 (m, 1 H, OH$\underline{CH_2}$C–), 3.35 (m, 1 H, –$CH_2\underline{OH}$), 3.19 (s, 1 H, –C$\underline{OH}$), 3.14 (dd, $J = 10.5$, 11.0 Hz, 1 H, –CH$\underline{CH_2}$O–), 1.45 (m, 1 H, –C$\underline{CH}(CH_2)CH_2$–), 1.02–1.08 (m, 10 H, –*t*Bu, –C$\underline{CH_2}$CH–), 0.45 (dd, $J = 6.0$, 6.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 100 MHz) δ 135.5, 135.4, 132.7, 132.7, 130.0, 130.0, 127.9, 66.5, 65.7, 60.5, 26.8, 26.2, 19.0, 16.4; HRMS (ESI) calcd for $C_{21}H_{28}O_3NaSi$: 379.16999, found for 379.17004 [$(M + Na)^+$].

(1*R*,2*S*)-[1-Benzoyloxy-1-benzoyloxymethyl-2-(*t*-butyldiphenylsilyloxy) methyl]-cyclopropane (21). To a solution of **17** (30.0 mg, 84.1 μmol) in pyridine (0.43 mL) was added BzCl (87 μL, 0.756 mmol) at room temperature. After stirring the mixture at room temperature for 3 h, the reaction mixture was partitioned between AcOEt and ice water. The organic layer was washed with saturated aqueous $NaHCO_3$, aqueous HCl (1 M) and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography

(5% AcOEt in hexane) to give **21** (43.2 mg, 76.6 μmol, 91%) as a colorless oil. [α]21D : −24.17 ($c = 1.67$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98–8.05 (m, 4 H, aromatic), 7.68 (m, 4 H, aromatic), 7.54 (m, 2 H, aromatic), 7.36–7.44 (m, 8 H, aromatic), 7.33 (dd, $J = 7.5$, 7.5 Hz, 2 H, aromatic), 5.03 (d, $J = 13.3$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.67 (d, $J = 13.3$ Hz, 1 H, –O$\underline{CH_2}$C–), 3.94 (m, 2 H, –C$\underline{H}$C$\underline{H_2}$O–), 1.70 (m, 1 H, –C$\underline{CH}$(CH$_2$)CH$_2$–), 1.30 (dd, $J = 10.5$, 6.8 Hz, 1 H, –C$\underline{CH_2}$CH–), 1.16 (dd, $J = 7.5$, 6.8 Hz, 1 H, –C$\underline{CH_2}$CH–), 1.05 (s, 9 H, –*t*Bu); 13C NMR ($CDCl_3$, 100 MHz) δ 166.3, 166.2, 135.6, 135.6, 133.4, 133.2, 133.0, 132,9, 130.2, 130.1, 129.7, 129.7, 129.7, 129.6, 128.3, 128.3, 127.7, 127.7, 65.6, 61.8, 60,7, 26.8, 25.9, 19.2, 15.5; HRMS (ESI) calcd for $C_{35}H_{36}O_5NaSi$: 587.22242, found for 587.22247 [$(M + Na)^+$].

{(1*R*,2*S*)-(1-Benzoyloxy-1-benzoyloxymehtyl-2-tosyloxymethyl)cyclopropane (4). To a solution of **21** (43.2 mg, 76.6 μmol) in THF (0.77 mL) was added a solution of tetrabutylammonium fluoride (1 M solution in THF, 0.12 mL, 0.12 mmol) at room temperature. After stirring the mixture at room temperature for 3 h, the solvent was evaporated in vacuo. The residue was partitioned between $CHCl_3$ and saturated aqueous NH_4Cl, and the organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. To the solution of the residue in pyridine (0.70 mL) was added TsCl (66.8 mg, 350 μmol) at 0 °C. After stirring the mixture at 0 °C for 8 h, the reaction mixture was partitioned between AcOEt and aqueous HCl (1 M). The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (20% AcOEt in hexane) to give **4** (23.7 mg, 49.3 μmol, 64%) as a colorless oil. [α]22D : −30.55 ($c = 1.06$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (m, 2 H, aromatic), 7.97 (m, 2 H, aromatic), 7.78 (d, $J = 8.0$ Hz, 2 H, aromatic), 7.52–7.57 (m, 2 H, aromatic), 7.37–7.44 (m, 4 H, aromatic), 7.27 (d, $J = 8.0$ Hz, 2 H, aromatic), 4.98 (d, $J = 13.3$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.43 (d, $J = 13.3$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.25 (m, 2 H, –CH$\underline{CH_2}$O–), 2.39 (s, 3 H, $\underline{CH_3}$Ph–), 1.84 (m, 1 H, –C$\underline{CH}$(CH$_2$)CH$_2$–), 1.42 (dd, $J = 10.3$, 7.4 Hz, 1 H, –C$\underline{CH_2}$CH–), 1.14 (dd, $J = 7.5$, 7.4 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 100 MHz) δ 165.9, 165.8, 144.8, 133.2, 133.0, 132.7, 129.8, 129.6, 129.5, 129.5, 128.3, 128.2, 127.7, 69.1, 64.4, 60.5, 22.5, 21.4, 16.5; HRMS (ESI) calcd for $C_{26}H_{24}O_7NaS$: 503.11349, found for 503.11331 [$(M + Na)^+$].

(1*R*,2*S*)-{1-Benzoyloxy-1-benzoyloxymethyl-2-[$N^{6'}$,$N^{6'}$-bis(*t*-butoxycarbonyl)-adenin-9-yl]methyl}cyclopropane (22a). To a solution of *N*,*N*-di-Boc-adenine (111 mg, 312 μmol) in DMF (1.0 mL) was added NaH (60% dispersion in mineral oil, 12.5 mg, 312 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the mixture was

added a solution of **4** (100 mg, 208 μmol) in DMF (1.0 mL) at room temperature. After stirring the mixture at 60 °C for 24 h, the reaction mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (33% AcOEt in hexane) to give **22a** (36.0 mg, 55.9 μmol, 27%) as a white solid. [α]22D : −1.18 ($c = 1.79$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (s, 1 H, adenine-H2), 8.34 (s, 1 H, adenine-H8), 8.05 (d, $J = 7.0$ Hz, 2 H, aromatic), 7.98 (d, $J = 7.0$ Hz, 2 H, aromatic), 7.58 (m, 2 H, aromatic), 7.40–7.47 (m, 4 H, aromatic), 5.14 (d, $J = 13.5$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.78 (d, $J = 13.5$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.65 (dd, $J = 14.9$, 6.8 Hz, 1 H, –CH$\underline{CH_2}$N–), 4.43 (dd, $J = 14.9$, 8.5 Hz, 1 H, –CH$\underline{CH_2}$N–), 2.07 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 1.46 (m, 19 H, –*t*Bu, –C$\underline{CH_2}$CH–), 1.32 (dd, $J = 7.5$, 7.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 166.2, 166.1, 150.5, 150.3, 133.4, 133.3, 129.7, 129.7, 129.5, 128.7, 128.5, 128.4, 83.7, 64.6, 60.9, 43.5, 27.8, 24.4, 16.8; HRMS (ESI) calcd for $C_{34}H_{37}O_8N_5Na$: 666.25343, found for 666.25320 [$(M + Na)^+$].

(1*R*,2*S*)-[1-Benzoyloxy-1-benzoyloxymethyl-2-(O^6-benzylguanin-9-yl) methyl]-cyclopropane (22b). To a solution of O^6-benzylguanine (75.3 mg, 312 μmol) in DMF (1.0 mL) was added NaH (60% dispersion in mineral oil, 12.5 mg, 312 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the resulting mixture was added a solution of **4** (100 mg, 208 μmol) in DMF (1.0 mL) at room temperature. After stirring the mixture at 50 °C for 24 h, the reaction mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (67% AcOEt in hexane) to give **22b** (41.0 mg, 74.6 μmol, 36%) as a white solid. [α]21D : −13.07 ($c = 2.05$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (d, $J = 7.5$ Hz, 2 H, aromatic), 7.93 (d, $J = 7.0$ Hz, 2 H, aromatic), 7.82 (s, 1 H, guanine-H8), 7.47–7.59 (m, 4 H, aromatic), 7.27–7.43 (m, 7 H, aromatic), 5.50 (d, $J = 12.5$ Hz, 1 H, –O$\underline{CH_2}$Ph), 5.44 (d, $J = 12.5$ Hz, 1 H, –O$\underline{CH_2}$Ph), 5.17 (d, $J = 13.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.94 (s, 2 H, –NH_2), 4.66 (d, $J = 13.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.39 (dd, $J = 15.0$, 7.5 Hz, 1 H, –CH$\underline{CH_2}$N–), 4.16 (dd, $J = 15.0$, 8.0 Hz, 1 H, –CH$\underline{CH_2}$N–), 2.04 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 1.44 (dd, $J = 10.3$, 7.2 Hz, 1 H, –C$\underline{CH_2}$CH–), 1.25 (dd, $J = 7.2$, 7.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 166.1, 166.0, 160.9, 159.2, 154.0, 138.8, 136.4, 133.3, 133.1, 129.6, 129.6, 129.6, 129.4, 128.4, 128.3, 128.1, 127.9, 67.9, 64.8, 60.7, 42.5, 24.2, 16.9; HRMS (ESI) calcd for $C_{31}H_{28}O_5N_5$: 550.20850, found for 550.20911 [$(M + H)^+$].

(1*R*,2*S*)-[2-(N^4-Benzoylcytosyn-1-yl)methyl-1-benzoyloxy-1-benzoyloxymethyl)-cyclopropane (22c). To a solution of N^4-benzoylcytosine (67.1 mg, 312 μmol) in DMF (1.0 mL) was added NaH (60% dispersion in mineral oil, 12.5 mg, 312 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the resulting mixture was added a solution of **4** (100 mg, 208 μmol) in DMF (1.0 mL) at room temperature. After stirring the mixture at 50 °C for 24 h, the reaction mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (33–67% AcOEt in hexane) to give **22c** (59.2 mg, 113 μmol, 54%) as a white solid. [α]19D : 0.09 ($c = 2.96$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.88 (br, 1 H, –NH), 7.98–8.01 (m, 5 H, aromatic,cytosine-H6), 7.90 (d, $J = 7.5$ Hz, 2 H, aromatic), 7.59 (t, $J = 7.5$ Hz, 1 H, aromatic), 7.55 (t, $J = 7.5$ Hz, 1 H, aromatic), 7.48–7.51 (m, 4 H, aromatic), 7.40–7.43 (m, 4 H, aromatic, cytosine-H5), 5.13 (d, $J = 13.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.67 (d, $J = 13.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.17 (m, 2 H, –CH$\underline{CH_2}$N–), 2.09 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 1.46 (dd, $J = 10.0$, 7.3 Hz, 1 H, –C$\underline{CH_2}$CH–), 1.28 (dd, $J = 7.3$, 7.0 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 166.1, 166.1, 162.2, 148.7, 133.3, 133.1, 133.0, 129.6, 129.6, 129.6, 129.4, 128.9, 128.9, 128.3, 128.1, 127.5, 125.2, 96.8, 64.9, 60.8, 49.6, 23.2, 16.7; HRMS (ESI) calcd for $C_{30}H_{25}O_6N_3Na$: 546.16356, found for 546.16390 [$(M + Na)^+$].

(1*R*,2*S*)-[1-Benzoyloxy-1-benzoyloxymethyl-2-(3-benzoylthymin-1-yl) methyl]-cyclopropane (22d). To a solution of N^3-benzoylthymine (17.0 mg, 74.0 μmol) in DMF (0.25 mL) was added NaH (60% dispersion in mineral oil, 2.96 mg, 74.0 μmol) at room temperature. After stirring the mixture at room temperature for 30 min, to the resulting mixture was added a solution of **4** (23.7 mg, 49.3 μmol) in DMF (0.25 mL) at room temperature. After stirring the mixture at 50 °C for 24 h, the reaction mixture was partitioned between 50% AcOEt in hexane and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by silica gel column chromatography (33–43% AcOEt in hexane) to give **22d** (20.5 mg, 38.1 μmol, 77%) as a white amorphous solid. [α]22D : 4.60 ($c = 1.94$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00–8.03 (m, 6 H, aromatic), 7.54–7.65 (m, 3 H, aromatic), 7.40–7.50 (m, 6 H, aromatic), 7.29 (s, 1 H, thymine-H6), 4.97 (d, $J = 13.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.69 (d, $J = 13.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 4.11 (m, 1 H, –CH$\underline{CH_2}$N–), 3.83 (m, 1 H, –CH$\underline{CH_2}$N–), 1.94 (m, 1 H, –C$\underline{CH}$(CH_2)CH_2–), 1.86 (s, 3 H, thymine-5–CH_3), 1.45 (dd, $J = 10.5$, 7.3 Hz, 1 H, –C$\underline{CH_2}$CH–), 1.15 (dd, $J = 7.5$, 7.3 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR ($CDCl_3$, 125 MHz) δ 169.1, 166.2,

163.1, 150.0, 134.9, 133.4, 133.3, 131.6, 130.6, 129.7, 129.6, 129.6, 129.5, 129.1, 128.4, 110.9, 77.2, 64.8, 60.7, 23.9, 16.1, 12.3; HRMS (ESI) calcd for $C_{31}H_{26}O_7N_2Na$: 561.16322, found for 561.16365 $[(M+Na)^+]$.

(1*R*,2*S*)-[2-(Adenine-9-yl)methyl-1-hydroxy-1-hydroxymethyl)cyclopropane (IVa). A solution of **22a** (36.0 mg, 55.9 μmol) in HCl (4.0 M in dioxane, 0.56 mL) was stirred at room temperature for 24 h, and the solvent was evaporated in vacuo. To a solution of the residue in MeOH (0.56 mL) was added a solution of NaOMe (5 M in MeOH, 30 μL, 150 μmol) at room temperature. After stirring the mixture at room temperature for 2 h, the reaction was quenched with aqueous HCl (1 M) and evaporated in vacuo. The residue was purified by NH silica gel column chromatography (5% MeOH in $CHCl_3$) to give **IVa** (8.24 mg, 35.0 μmol, 62%) as a white solid. mp 157–161 °C; [α]19D : −10.00 ($c = 0.48$, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 8.27 (s, 1 H, adenine-H2), 8.20 (s, 1 H, adenine-H8), 4.28 (dd, $J = 15.3$, 7.0 Hz, 1 H, –CHC$\underline{H_2}$N–), 4.24 (dd, $J = 15.3$, 8.3 Hz, 1 H, –CHC$\underline{H_2}$N–), 4.00 (d, $J = 12.5$ Hz, 1 H, –OC$\underline{H_2}$C–), 3.70 (d, $J = 12.5$ Hz, 1 H, –OC$\underline{H_2}$C–), 1.64 (m, 1 H, –CC$\underline{H}$(CH_2)C$\underline{H_2}$–), 0.96 (dd, $J = 10.0$, 6.0 Hz, 1 H, –CC$\underline{H_2}$CH–), 0.69 (dd, $J = 6.5$, 6.0 Hz, 1 H, –CC$\underline{H_2}$CH–); 13C NMR (CD_3OD, 125 MHz) δ 157.3, 153.6, 150.5, 142.8, 119.9, 65.3, 60.2, 44.7, 25.8, 16.6; HRMS (ESI) calcd for $C_{10}H_{14}O_2N_5$: 236.11420, found for 236.11415 $[(M+H)^+]$.

(1*R*,2*S*)-[2-(Cytosyn-1-yl)methyl-1-hydroxy-1-hydroxymethyl]cyclopropane (IVc). To a solution of **22c** (59.2 mg, 113 μmol) in MeOH (1.0 mL) was added a solution of NaOMe (5 M in MeOH, 91 μL, 455 μmol) at room temperature. After stirring the mixture at room temperature for 2 h, the reaction was quenched with aqueous HCl (1 M) and evaporated in vacuo. The residue was purified by NH silica gel column chromatography (9–17% MeOH in $CHCl_3$) to give **IVc** (17.1 mg, 81.0 μmol, 72%) as a white solid. mp 180–181 °C; [α]19D : −27.72 ($c = 0.75$, CH_3OH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.71 (d, $J = 7.3$ Hz, 1 H, cytosine-H6), 5.86 (d, $J = 7.3$ Hz, 1 H, cytosine-H5), 3.91 (d, $J = 12.5$ Hz, 1 H, –OC$\underline{H_2}$C–), 3.87 (dd, $J = 14.3$, 8.0 Hz, 1 H, –CHC$\underline{H_2}$N–), 3.75 (dd, 1 H, $J = 14.3$, 7.0 Hz, –CHC$\underline{H_2}$N–), 3.62 (d, $J = 12.5$ Hz, 1 H, –OC$\underline{H_2}$C–), 1.49 (m, 1 H, –CC$\underline{H}$(CH_2)C$\underline{H_2}$–), 0.89 (dd, $J = 10.3$, 5.9 Hz, 1 H, –CC$\underline{H_2}$CH–), 0.58 (dd, $J = 7.0$, 5.9 Hz, 1 H, –CC$\underline{H_2}$CH–); 13C NMR (CD_3OD, 125 MHz) δ 167.9, 159.3, 147.4, 95.8, 65.6, 60.2, 50.2, 49.2, 25.3, 16.3; HRMS (ESI) calcd for $C_9H_{14}O_3N_3$: 212.10297, found for 212.10327 $[(M+H)^+]$.

(1*R*,2*S*)-[2-(Thymin-1-yl)methyl-1-hydroxy-1-hydroxymethyl]cyclopropane (IVd). To a solution of **22d** (20.1 mg, 34.8 μmol) in MeOH (0.34 mL) was added a solution of NaOMe (5 M in MeOH, 28 μL, 140 μmol) at room temperature. After stirring the mixture at room temperature for 2 h, the reaction mixture was quenched with aqueous HCl (1 M) and evaporated in

vacuo. The residue was purified by NH silica gel column chromatography (7–10% MeOH in $CHCl_3$) to give **IVd** (7.25 mg, 32.1 μmol, 92%) as a white amorphous solid. [α]20D : −21.84 ($c = 0.56$, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 7.57 (s, 1 H, thymine-H6), 3.93 (d, $J = 12.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 3.81 (dd, $J = 14.4$, 7.5 Hz, 1 H, –CH$\underline{CH_2}$N–), 3.73 (dd, 1 H, $J = 14.4$, 7.3 Hz, –CH$\underline{CH_2}$N–), 3.60 (d, $J = 12.0$ Hz, 1 H, –O$\underline{CH_2}$C–), 1.88 (s, 3 H, thymine-5–CH_3), 1.48 (m, 1 H, –C$\underline{CH}(CH_2)CH_2$–), 0.91 (dd, $J = 10.0$, 5.8 Hz, 1 H, –C$\underline{CH_2}$CH–), 0.60 (dd, $J = 6.5$, 5.8 Hz, 1 H, –C$\underline{CH_2}$CH–); 13C NMR (CD_3OD, 125 MHz) δ 166.9, 153.2, 143.2, 111.1, 65.6, 60.1, 48.7, 25.1, 16.5, 12.2; HRMS (ESI) calcd for $C_{10}H_{14}O_4N_2Na$: 249.08458, found for 249.08463 [$(M + Na)^+$].

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