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# Synthesis, Antiviral Evaluation, and Computational Studies of Cyclobutane and Cyclobutene L-Nucleoside Analogues

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This paper describes the stereoselective synthesis of a series of functionalized cyclobutane and cyclobutene L-nucleoside analogues featuring a methylene spacer between the carbocycle and the nucleobase. These L-nucleoside analogues were subjected to comprehensive screening for antiviral activity. To obtain knowledge at the molecular structural level relevant for designing future analogues, the mechanism of action of these L-nucleoside analogues as anti-herpes simplex virus agents was investigated by computational approaches. In particular, protein–ligand docking calculations were used to rationalize the ability of the prodrug candidates to be activated. Docking experiments were performed on the three kinases involved in the activation process of thymine and guanine derivatives.

## Introduction

The application of nucleoside analogues (NAs) in antiviral therapy has evolved into an important option over the last three decades.[1] However, the emergence of drug-resistant mutants that render current therapies ineffective[2] drives research into the development of new nucleoside analogues with high potency, low toxicity, and favourable resistance profiles. The search for more active nucleoside analogues has primarily focussed on modifications of the carbohydrate moiety.

In this regard, carbocyclic analogues of natural nucleosides have played a major role in the development of new antiviral agents. These analogues are more resistant to hydrolytic processes, and they have a greater lipophilicity than natural nucleosides, which favours absorption and penetration through the cell membrane. Additionally, the conformational properties of carbocyclic nucleoside analogues are often different from those of standard furanose-derived nucleosides. The cyclopentenyl nucleosides Carbovir (**1**)[3] and Abacavir (**2**),[4] and the cyclobutyl nucleoside Lobucavir (**3**),[5] are some of the earlier successful examples (Figure 1). Since the high antiviral activity of Lobucavir was discovered, the synthesis of cyclobutane nucleoside analogues and also their antiviral activity have been the subject of close scrutiny by several research groups, including ours.[6]

Other modifications have led to the discovery that L-nucleoside analogues (L-NAs) have antiviral activity.[7] Several of these analogues, such as Lamivudine (**4**),[8] Emtricitabine (**5**),[9] and Telbivudine (**6**),[10] have been shown to have potent activities against a wide range of viral infections, and also to have mild toxicities. The fact that some unnatural L-nucleosides show antiviral activity indicates that not all of the enzymes involved in phosphorylation processes are completely enantioselective. Actually, this relaxed enantioselectivity has been perceived as a potential antiviral strategy, favouring the use of L-nucleosides, since they may provide a better toxicological profile and a greater stability against cellular enzymes than their D-counterparts.[11]

In recent years, our laboratory has exploited the [2+2] photochemical cycloaddition of homochiral α,β-unsaturated γ-lactones to alkenes for the stereoselective synthesis of a variety of enantiopure four-membered-ring-containing natural products.[12,13] Based on our previous experience and on the promising antiviral activities of L-nucleosides, we became interested in developing new strategies to prepare a series of unprecedented cyclobutane and cyclobutene L-nucleoside analogues. In this paper, we describe the synthesis and antiviral activity of the cyclobutane and cyclobutene L-NAs **7**–**11**. These analogues, besides having different functionality in the cyclobutane unit, feature a methylene spacer between the nucleobase and the cyclobutane moiety, and also bear an additional hydroxymethyl group. Moreover, to rationalize the experimentally observed activities,

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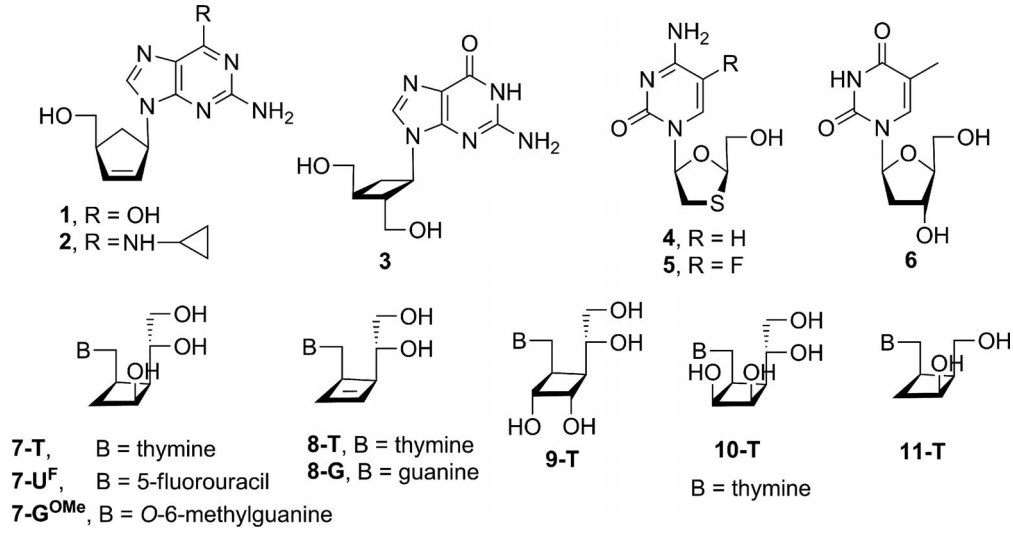



Figure 1. Selected carbocyclic and L-nucleoside analogues **1**–**6**, and synthesized cyclobutane L-nucleoside analogues **7**–**11**.

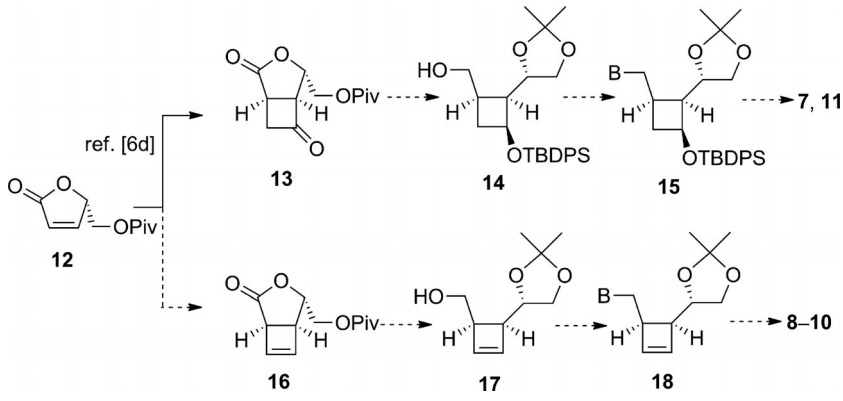
we combined our synthetic work with molecular modelling, specifically, structural studies of the synthesized analogues in the active sites of viral and cellular kinases.

## Results and Discussion

Our synthetic plan (Scheme 1) involved the diastereoselective construction of the cyclobutane or cyclobutene ring by a [2+2] photochemical reaction of enantiopure 2(5*H*)-furanone **12**, followed by the conversion of the cycloadducts (i.e., **13** and **16**) into key intermediates **14** and **17**. It was envisaged that both alcohols **14** and **17** would be suitable substrates for the introduction of the selected nucleobases by Mitsunobu reaction to produce **15** and **18**, and eventually the carbocyclic L-nucleoside analogues (i.e., **7**–**11**).

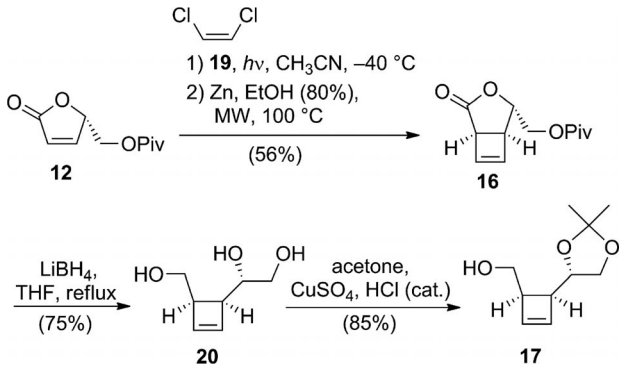
Accordingly, our initial efforts focussed on the preparation of pivotal intermediates **14** and **17**. The synthesis of cyclobutene intermediate **17** (Scheme 2) started with the [2+2] photocycloaddition of pivaloyl-protected 2(5*H*)-furanone **12**[14] to (*Z*)-1,2-dichloroethylene (**19**), followed by a reductive elimination reaction with activated Zn in 80% EtOH[15] under microwave irradiation to give bicycle **16**, derived from the major *anti*-configured cycloadducts, in 56% overall yield. Formation of triol **20** by exhaustive reduction of **16** was accomplished in 75% yield using $LiBH_4$ in THF at reflux temperature. Subsequent protection of the 1,2-diol moiety was achieved by treatment of **20** with acetone under acid catalysis in the presence of $CuSO_4$ to give cyclobutene intermediate **17** in excellent yield. Known alcohol **14** was prepared in a similar way in 28% yield from **12**, following our previously described synthetic sequence, which was refined and improved (see Supporting Information).[6d]

Next, we turned our attention to the introduction of the base moiety. First, we undertook the synthesis of pyrimidine cyclobutane analogues starting from **14** (Scheme 3). Thus, the Mitsunobu reaction[16] of **14** with *N*3-benzoylthymine[17] using $PPh_3$ and DBAD (di-*tert*-butyl azodicarboxylate) in THF at reflux temperature delivered **21** in 73% yield. Fluorine-containing nucleoside analogue **22** was prepared in 62% yield in the same manner by treatment of alcohol **14** with *N*3-benzoyl-5-fluorouracil.[17,18] It is worth noting that the reaction of the bases with the corresponding mesylate in a classical $S_N2$ reaction gave lower yields of **21** and **22**. That the base was linked at *N*1 in **21** and **22** was confirmed from their HMBC spectra, which showed corre-




Scheme 1. Strategy for the synthesis of cyclobutane and cyclobutene L-NAs. TBDPS = *tert*-butyldiphenylsilyl.

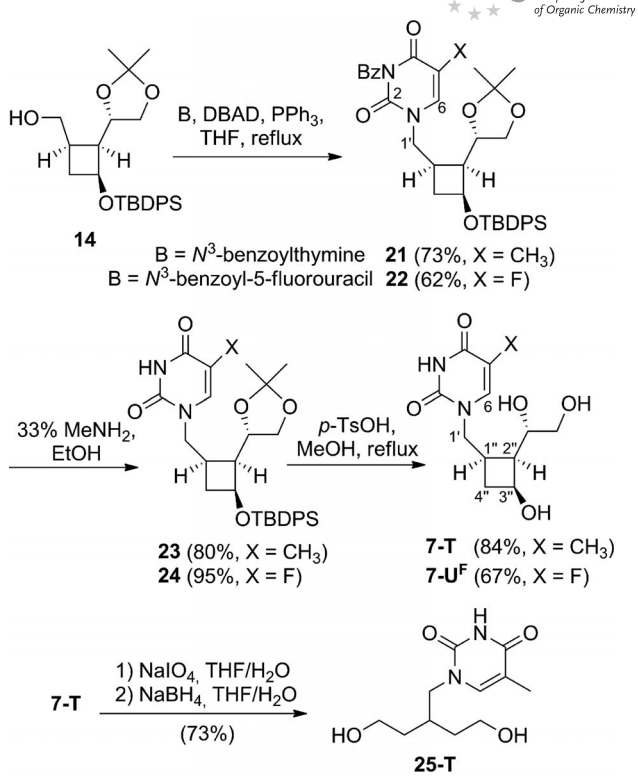



Scheme 2. Synthesis of intermediate **17**. MW = microwave irradiation.

lations between 1′-H and both C-2 and C-6, and also between C-1′ and 6-H. The syntheses of L-nucleoside analogues **7-T** and **7-U$^F$** from **21** and **22** required deprotection of *N*3 and of the three hydroxy groups. First, cleavage of the *N*3-protecting group was achieved by reaction of **21** with $MeNH_2$ (33% solution in EtOH).[17] The reaction proceeded smoothly at room temp. to give **23** in 80% yield. Next, simultaneous removal of the acetonide and silyl ether protecting groups by treatment of **23** with *p*TsOH in MeOH at reflux temperature gave target nucleoside analogue **7-T** in 84% yield. The synthesis of fluorouracil nucleoside analogue **7-U$^F$** was carried out in an analogous manner in 64% yield over the two steps. The NOESY spectra of **7-T** and **7-U$^F$** proved the relative configuration of the stereogenic centres of the cyclobutane ring, since the 1′′-H proton showed cross-peaks with 3′′-H and 4′′-H.

We then undertook the synthesis of hydroxymethyl derivative **11-T**, which we anticipated would be achieved by the oxidative cleavage of the diol present in **7-T**, followed by reduction of the resulting aldehyde. However, when diol **7-T** was subjected to the standard conditions of oxidative cleavage and reduction, only acyclic compound **25-T** was isolated in 73% yield (Scheme 3). The formation of **25-T** can be rationalized in terms of a retro-aldol reaction of the originally formed β-hydroxy aldehyde, followed by the reduction of both aldehyde groups. To avoid the formation of this acyclic product, other oxidative cleavage conditions were explored. Our attempts, including treatment with $Pb(OAc)_4$ or $Mn(OAc)_3$,[19] or with a combination of $KIO_4$ and $KHCO_3$ in a buffered solution at pH 7–7.5,[20] either led to **25-T** or gave complex mixtures of products.

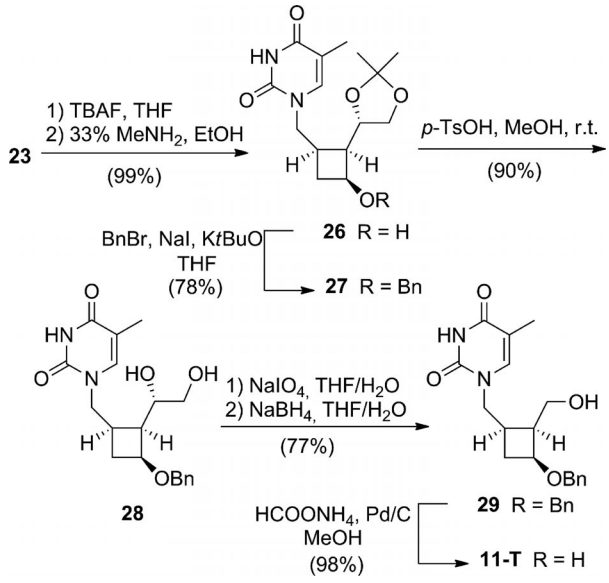
In the light of these results, we pursued an alternative route to **11-T**, keeping the cyclobutane alcohol protected during the oxidative cleavage step to guarantee the integrity of the cyclobutane moiety (Scheme 4). Desilylation of **23** with TBAF (tetrabutylammonium fluoride) followed by nucleobase deprotection gave alcohol **26** in almost quantitative yield. Benzylation of the hydroxy group of **26** was accomplished by treatment with BnBr, NaI, and *t*BuOK in THF. Next, **27** was exposed to mildly acidic conditions to induce hydrolysis of the acetonide group and deliver diol **28** in 90% yield. This diol was submitted to an oxidative cleavage and subsequent reduction to give the corresponding hydroxymethyl derivative (i.e., **29**) in 77% yield. Finally, cleavage of the benzyl ether by catalytic hydrogen-transfer reduction[21] using ammonium formate in the presence of 10% Pd/C in MeOH delivered target nucleoside analogue **11-T** in almost quantitative yield. Its stereochemical assignment was made on the basis of 1D and 2D NMR spectroscopy, and was further confirmed by X-ray crystallographic analysis.



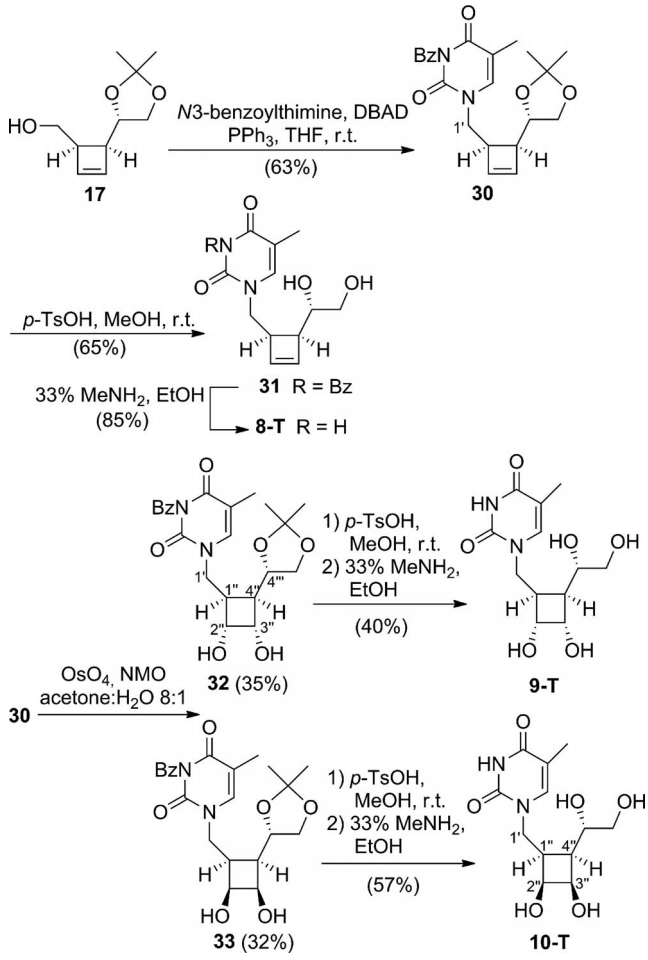

Scheme 3. Preparation of cyclobutane L-NAs **7-T** and **7-U$^F$**, and attempted oxidative cleavage of **7-T**.

We then directed our attention to the preparation of cyclobutene thymine analogue **8-T** (Scheme 5). Thus, after the coupling reaction of *N*3-benzoylthymine with alcohol **17**, removal of both the acetal and benzoyl protecting groups of **30** delivered target cyclobutene nucleoside analogue **8-T** in 35% overall yield. At this point, we decided to further functionalize the cyclobutane double bond. To this end, fully protected compound **30** was subjected to dihydroxylation under mild conditions[22] by reaction with NMO (*N*-methylmorpholine *N*-oxide) and catalytic $OsO_4$ in acetone/$H_2O$ to give a chromatographically separable mixture of diols **32** and **33** in 35 and 32% yields, respectively. The relative configuration of diol **32** was assigned on the basis of NOE experiments that showed enhancement of the cyclobutane 3′′-H proton upon irradiation of 4′′′-H. Unfortunately, the chemical shifts of the key protons in **33** were almost identical, and so unambiguous NOE signals between them could not be determined. The relative configuration of **33** was proved after its conversion into compound **10-T**. Thus, sequential removal of the acetonide and benzoyl protecting groups from **32** and **33** gave cyclobutane tetrol L-




Scheme 4. Preparation of cyclobutane L-NA **11-T**.




Scheme 5. Preparation of cyclobutene and cyclobutane L-NAs **8-T**, **9-T**, and **10-T**.

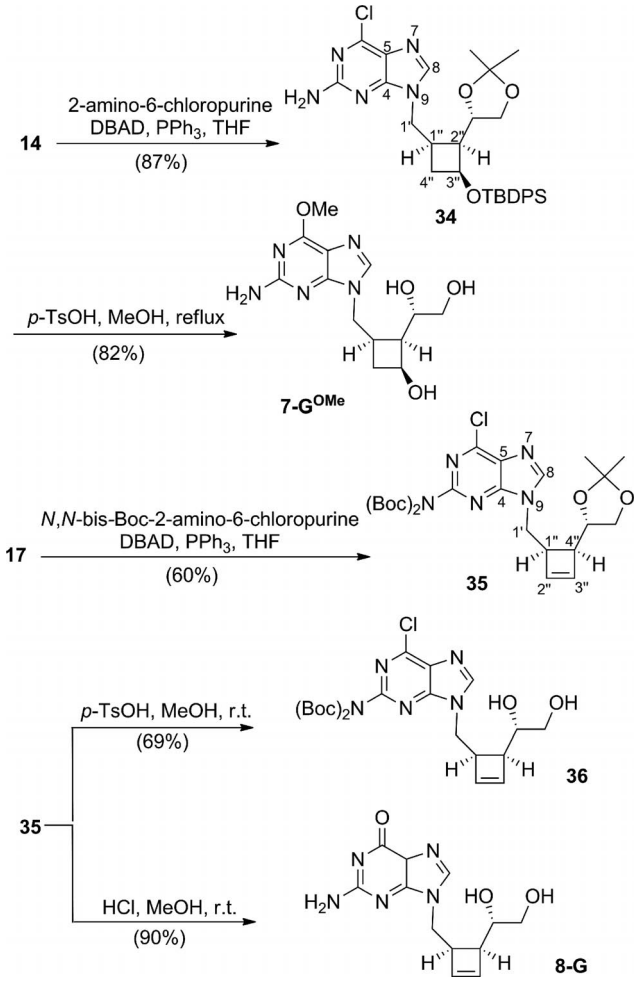
NAs **9-T** and **10-T** in 40 and 57% yields, respectively. NOE analysis of **10-T** revealed its relative configuration. Hence, irradiation of the 4′′-H proton led to selective enhancements of 2′′-H and 3′′-H, indicating that these protons are on the same side of the ring.

Next, we focussed on the synthesis of purine cyclobutane and cyclobutene L-nucleoside analogues starting from **14** and **17**, following a strategy similar to that described above (Scheme 6). The Mitsunobu reaction of alcohol **14** with 2-amino-6-chloropurine, which was chosen because of its easy conversion into either guanine[23] or its 6-*O*-methyl derivative,[24,25] exclusively gave the *N*9 regioisomer (i.e., **34**) in excellent yield (87%). The attachment site of the purine base was established by HMBC experiments, which showed a correlation between the C-4 carbon and the 1′-H proton. We targeted the $O^6$-methylguanine derivative to give an analogue with higher lipophilicity, which can result in an improved cellular uptake.[24,26] To this end, compound **34** was treated with *p*TsOH in MeOH at reflux temperature. Under these conditions, in addition to the expected alcohol deprotection, the chlorine was replaced by a methoxy group, and the target nucleoside analogue (i.e., **7-G$^{OMe}$**) was obtained in good yield.[27]

The synthesis of guanine cyclobutene analogue **8-G** was carried out from **17** in a similar manner. However, since the coupling reaction of **17** with unprotected 2-amino-6-chloropurine gave poor yields, the reaction was performed with its *N*,*N*-bis-Boc-protected derivative (Boc = *tert*-butoxycarbonyl; Scheme 6).[28] Fortunately, with this substrate, the Mitsunobu reaction proceeded smoothly to deliver **35** in 60% yield. We assumed that **35** could be directly converted into the corresponding guanine derivative (i.e., **8-G**) by simultaneous removal of the bis-Boc and acetonide protections and chlorine–oxygen exchange by treatment with aqueous trifluoroacetic acid (TFA).[29] However, exposure of **35** to TFA/$H_2O$ (3:1) led to a complex mixture of unidentified products. On the other hand, treatment of **35** with *p*TsOH in MeOH at room temp. for 30 min generated diol **36** exclusively, with no effect on the 6-chloro or the Boc protecting groups. Eventually, it was found that **35** could be converted into **8-G** in excellent yield by treatment with HCl in MeOH at room temp.[30]

Compounds **7-T**, **7-U$^{F}$**, **7-G$^{OMe}$**, **8-T**, **8-G**, **9-T**, **10-T**, **25-T**, and **36** were subjected to comprehensive screening for antiviral activity. They were tested for antiviral activity in human embryonic lung (HEL) cell cultures [herpes simplex virus-1 (HSV-1; strain KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, and herpes simplex virus-1 (KOS thymidine kinase-deficient acyclovir resistant)], in HeLa cell cultures [vesicular stomatitis virus, coxsackie virus B4, and respiratory syncytial virus], in Vero cell cultures [parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, and Punta Toro virus], in Crandell–Rees feline kidney (CRFK) cell cultures [feline corona virus and feline herpes virus], and in Madin–Darby canine kidney (MDCK) cell cultures [influenza A virus (H1N1, H3N2) and influenza B virus]. None of the compounds showed significant antiviral activity or cytotoxicity.[31]




Scheme 6. Preparation of cyclobutane and cyclobutene L-NAs **7-G$^{OMe}$** and **8-G**.

To gain antiviral activity, the prepared L-NAs require serial phosphorylation, via mono- and diphosphate intermediates, to give the biologically active triphosphorylated form L-NA-TP.[32] So bearing in mind that the L-NAs have a cyclobutane moiety and an inverted configuration, the activity of the cyclobutane L-NAs would be dependent on the ability of all the enzymes of the activation pathway to phosphorylate analogues with carbocyclic scaffolds with opposite chirality, as well as the ability of the resulting L-NA-TP to successfully interact with the DNA polymerase. The conversion of the L-NAs into their active L-NA-TPs is as important as the affinity of these analogues for the target DNA polymerase. Often, the first phosphorylation reaction is the rate-limiting step, because of the specificity of the nucleoside kinase involved, and this step could be bypassed by the preparation of pronucleotides.[33] However, before we carried out further chemical synthesis, we decided to discern whether the phosphorylation of our analogues may be a requirement for antiviral activity. To this end, we undertook a molecular modelling study of compounds **7**–**10** and **25** on the whole activation process, focussing on HSV-1. To the best of our knowledge, this is the first study that investigates the three successive phosphoryl transfers to NAs in HSV-1 infected cells.

Molecular docking simulations were performed using the program GOLD (version 5.0)[34] on all of the enzymes involved in the activation process of the aforementioned compounds: HSV-1 thymidine kinase (HSV-1 TK) for the first phosphorylation step; HSV-1 TK and guanylate kinase (GMPK) for the second phosphorylation step of thymine and guanine derivatives, respectively; and finally nucleoside diphosphate kinase (NDPK) for the third phosphorylation step.[35] In each case, calculations were carried out using crystal structures that have been solved with natural ligands, such as thymidine and guanosine, or with the drug acyclovir. It is important to note that carbocyclic nucleoside analogues **7**–**10** contain an additional hydroxymethyl moiety compared to natural nucleosides. As a result, two different activation pathways were envisaged, in which the three successive phosphoryl transfers could take place either at 1′′′-OH or 2′′′-OH (Figure 2). Compounds **7**–**10** and **25** were docked separately into the active site of each kinase in their reactive forms. Calculations with thymidine (dT) and acyclovir (ACV) were also performed to give structural and energetic benchmarks for pyrimidine and purine compounds, respectively. The docking results were analysed in structural and energetic terms. The main criterion was to check that a substantial number of low-energy binding modes were consistent with a precatalytic orientation,[36] and that the corresponding binding energies were similar to or even lower than those of the reference compounds.

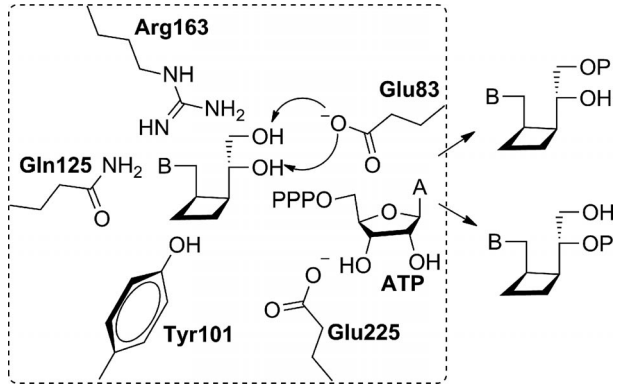



Figure 2. Representation of the two possible phosphorylation pathways of the compounds studied. An example is given for the first kinase involved in the activation process (HSV-1 thymidine kinase): upon abstraction of the corresponding proton by Glu83, nucleoside analogues may be phosphorylated at either their 1′′′ or 2′′′ position. ATP = adenosine triphosphate.

The first phosphorylation step was studied on the HSV-1 TK structure crystallized with dT in its binding site [PDB (protein data bank) entry code: 1KIM[37]] for thymine derivatives, and HSV-1 TK crystallized with ACV (PDB entry code: 2KI5[38]) for guanine derivatives. Docking calculations of the synthetic nucleoside analogues led to three different behaviours (Tables S7 and S8, Supporting Infor-

mation). Compounds **7-T**, **8-T**, **8-G**, **9-T**, **10-T**, and **25-T** showed predicted binding modes similar to those of crystallographic dT and ACV. All these nucleoside analogues gave low-energy solutions in which both 1′′′-OH and 2′′′-OH interacted with the catalytic residue Glu83, which is responsible for deprotonating the alcohol to be phosphorylated, which suggests that both phosphorylation pathways could take place (Figure 3, a).[35] Conversely, the lowest energy binding modes of compound **7-U$^{F}$** are consistent with catalytic reactivity of the enzyme, but its best oriented structure has a binding energy higher than that of dT. As a consequence, it is not possible to be sure that the phosphorylation of this compound would be successful. Finally, compound **7-G$^{OMe}$** is not expected to be phosphorylated by HSV-1 TK, because of the clashes with Gln125 and Arg176 that prevent the right orientation for the catalytic reaction (Figure 3, b). This compound flips around to minimize these clashes, leaving either the base or the hydroxy moieties outside their respective binding pockets. Therefore, the presence of a modified purine base in the studied compounds seems to be restrictive for the first activation step.

The second phosphorylation step is carried out by different kinases depending on the nature of the nucleoside base: HSV-1 TK for thymine derivatives, and GMPK for guanine derivatives.[35] The lack of human GMPK crystallographic structures prompted us to use the mouse GMPK structure to study the guanine derivatives. The high sequence similarity between mouse and human GMPK allows the assumption that the information on the mouse enzyme is directly transferable to the human enzyme.[39] Accordingly, the structures selected to perform the calculations on this second activation step were: HSV-1 TK crystallized with thymidine-5′-monophosphate (dTMP) and adenosine diphosphate (ADP) (PDB entry code: 1VTK[40]); and mouse GMPK with guanylate-5′-monophosphate (GMP) and ADP in its binding site (PDB entry code: 1LVG[39]). Molecular docking calculations of monophosphorylated nucleoside analogues **7-T**, **7-U$^{F}$**, **8-T**, **8-G**, **9-T**, **10-T**, and **25-T** showed different profiles (Tables S9 and S10, Supporting Information). Compounds **7-T**, **8-T**, and **8-G** may be phosphorylated either at their 1′′′ or 2′′′ position, with the calculate structures corresponding to all of these reactions maintaining the main interactions of the corresponding X-ray structures (Figure 4). In contrast, compound **10-T** is expected to be activated only at its 1′′′ position. Lastly, compounds **7-U$^{F}$**, **9-T**, and **25-T** clearly fail to be activated by HSV-1 TK, since few of their binding modes are similar to the crystallographic ones, and their binding energies are higher than that of the reference compound.

Regarding the last activation step, X-ray structures of human NDPK are only available with purine derivatives, which make them unsuitable for docking with pyrimidine analogues. In fact, docking calculations of dT on these structures led to inconsistent binding modes. Therefore, docking calculations were performed on two different crystallographic structures: for pyrimidine derivatives, a complex of slime mould *Dictyostelium discoideum* NDPK with

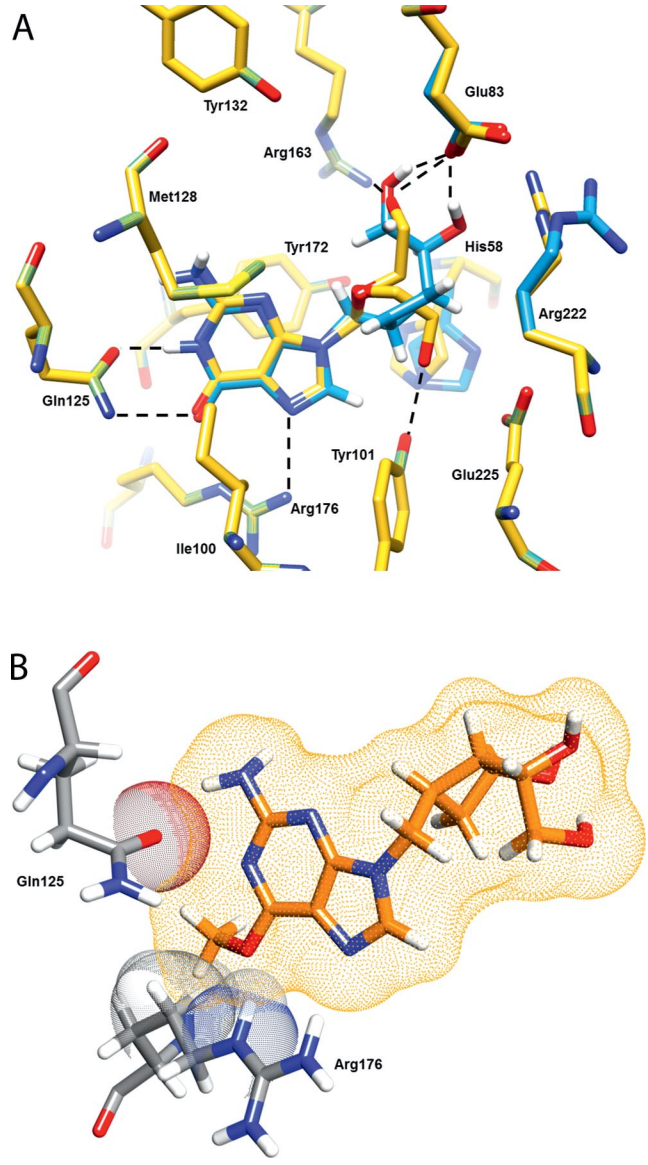



Figure 3. a) Overlap between the best binding mode of compound **8-G** (blue) and crystallographic ACV (yellow) in the HSV-1 TK binding site (PDB entry code: 2KI5). Hydrogen bonds between ligands and residues are shown as dotted lines. b) Steric clashes between compound **7-G$^{OMe}$** and Gln125 and Arg176 in the HSV-1 TK binding site (PDB entry code: 2KI5). Van der Waals radii of the atoms involved in the clashes are shown with dots.

thymidine-5′-diphosphate (dTDP) (PDB entry code: 1NDC[41]), which has in many respects shown behaviour similar to that of its human counterpart; and for purine derivatives, human NDPK crystallized with guanosine-5′-diphosphate (GDP) (PDB entry code: 1NUE[42]). It is worth pointing out that since the binding sites of both NDPKs are quite exposed to solvent,[43] docking calculations of the X-ray ligands into the corresponding structures do not reproduce the crystallographic structures as well as was seen for the previous activation steps. Thus, the predictions for this activation step should be read with caution. According to docking studies, the diphosphorylated derivatives of **7-T**, **8-T**, **10-T**, and **8-G** show some binding modes

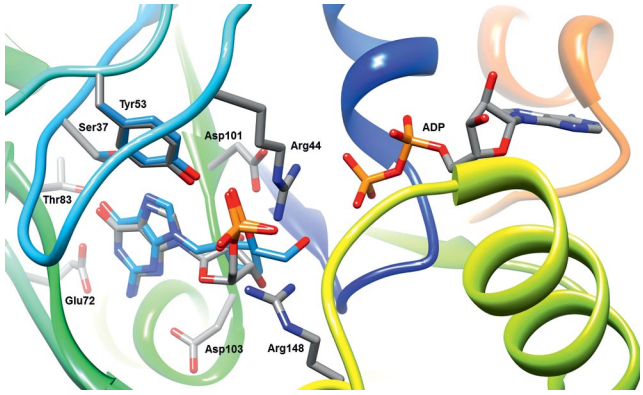



Figure 4. Overlap between the best binding mode of monophosphorylated **8-G** (blue) and crystallographic GMP (gray) in the mouse GMPK binding site (PDB entry code: 1LVG). Crystallographic ADP is also shown. Hydrogen atoms and hydrogen bonds are not shown for clarity.

consistent with catalysis. Therefore all these analogues are likely to be phosphorylated to their active form by NDPK (Figure 5, Tables S11 and S12, Supporting Information).

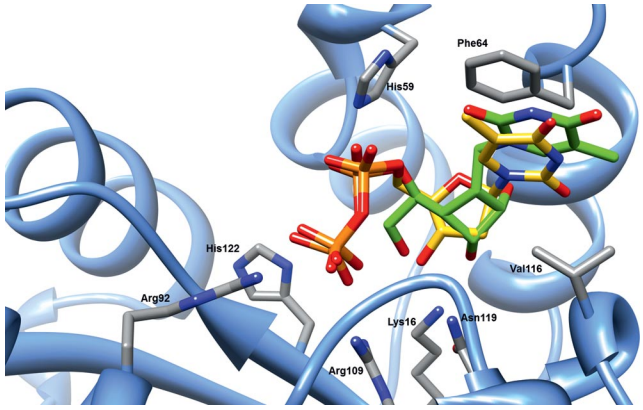



Figure 5. Overlap between the best binding mode of diphosphorylated **8-T** (green) and crystallographic dTDP (yellow) in the *Dictyostelium discoideum* NDPK binding site (PDB entry code: 1NDC). Hydrogen atoms are not shown for clarity.

## Conclusions

A synthetic strategy for the stereoselective preparation of several enantiopure functionalized cyclobutane L-nucleoside analogues with a methylene spacer between the nucleobase and the cyclobutane is presented. The synthesized cyclobutane L-NAs were subjected to comprehensive screening for antiviral activity. None of the compounds showed significant antiviral activity or cytotoxicity. Molecular modelling studies on the synthesized analogues were performed on the whole activation process to find out whether a failure to undergo this activation process could be the cause of their poor activity against HSV-1. The theoretical results show that the activation process clearly fails for nucleoside analogues **7-U$^{F}$**, **7-G$^{OMe}$**, **9-T**, and **25-T**, whereas compounds **7-T**, **8-T**, **8-G**, and **10-T** may be able to be activated. Assuming that the latter analogues are converted into their active forms, the lack of activity against HSV-1 might be due either to chemical deactivation of their triphosphorylated forms, or to a failure in their incorporation into the viral DNA strand, carried out by HSV-1 DNA polymerase. Unfortunately, it has not been possible to study this last process, due to the lack of HSV-1 DNA polymerase structures crystallized with DNA. Work is in progress to use homology modelling to generate such a complex.

## Experimental Section

**General Remarks:** Commercially sourced reagents were used as received. Solvents were dried by distillation over the appropriate drying agents. All reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 pre-coated aluminum plates (0.20 mm thickness), or by GC when necessary. Flash column chromatography was performed using silica gel (230–400 mesh) unless otherwise indicated. Filtrations through basic anion-exchange resins were carried out using Dowex® 1X8 resin (chloride form, 20–50 mesh). Filtrations through acidic cation-exchange resins were performed using Dowex® 50WX8 resin (hydrogen form, 200–400 mesh). $^{1}$H and $^{13}$C NMR spectra were recorded at 250, 360, 400, or 600 MHz, and 62.5, 90, or 100 MHz, respectively. Proton chemical shifts are reported in ppm on the $\delta$ scale ($CDCl_3$, $\delta$ = 7.26; [$D_4$]methanol, $\delta$ = 3.31 ppm). Carbon chemical shifts are reported in ppm on the $\delta$ scale ($CDCl_3$, $\delta$ = 77.2; [$D_4$]-methanol, $\delta$ = 49.0 ppm). NMR signals were assigned with the help of COSY, HSQC, HMBC, DEPT135, and some NOE and NOESY experiments. Infrared peaks are reported in $cm^{-1}$. Melting points were determined with a hot stage apparatus. Optical rotations were measured at 22 ± 2 °C.

Microwave reactions were conducted using a CEM Discover™ microwave synthesizer. The machine consists of a continuous focussed microwave-power delivery system with an operator-selectable power output from 0 to 300 W. The temperature of the contents of the vessel was monitored using a calibrated infrared temperature control mounted under the reaction vessel. In all experiments, the contents of the vessel were stirred using a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stirrer bar in the vessel.

**Antiviral Activity Assays:** The compounds were evaluated against the following viruses: herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK–) HSV-1 KOS strain resistant to ACV (ACVr), herpes simplex virus type 2 (HSV-2) strains Lyons and G, vaccinia virus Lederle strain, respiratory syncytial virus (RSV) strain Long, vesicular stomatitis virus (VSV), Coxsackie B4, parainfluenza 3, influenza virus A (subtypes H1N1 and H3N2), influenza virus B, reovirus-1, Sindbis, and Punta Toro virus. The antiviral assays were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey cells (Vero), human epithelial cells (HeLa), Crandell-Rees feline kidney cells (CRFK), or Madin–Darby canine kidney cells (MDCK). Confluent cell cultures in microtitre 96-well plates were inoculated with 100 $CCID_{50}$ of the virus (1 $CCID_{50}$ being the dose of the virus sufficient to infect 50% of the cell cultures) in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation was recorded as soon as it reached completion in the control virus-infected cell cultures that had not been treated with the test com-

pounds. Antiviral activity is expressed as $EC_{50}$, i.e., the compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%.

**Molecular Modelling:** The binding modes and energies were predicted using protein–ligand docking algorithms. The calculations were performed with the docking program GOLD (version 5.0.1).[34] The Chemscore scoring function was used.[44,45] The structures of the ligands were initially optimized using the Marvin[46] work package and MMFF minimization. For each PDB structure, all waters of crystallization, ions, and crystallized ligands were removed. Geometrical and hydrogen-bonding criteria were used to decide which rotamer of the residues was considered for the calculations. For each enzyme, the centre of the binding site in the crystallographic structure was used as the central point for the cavity. The structural flexibility of the receptor was taken into account for a series of residues in the binding pocket using the free rotation scheme of the GOLD program. Ligand flexibility was also considered for all the compounds studied. Each compound was docked into the corresponding enzyme and 20 predicted orientations were obtained.

**(1*R*,4*S*,5*S*)-4-Pivaloyloxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (16):** A solution of lactone **12** (1.83 g, 9.25 mmol) and (*Z*)-1,2-dichloroethylene (**19**; 3.5 mL, 46.39 mmol) in acetonitrile (937 mL) was placed in a photochemical reactor (two-necked 1 L vessel fitted with a Quartz immersion-type cooling jacket). The reaction mixture was initially degassed by passing oxygen-free nitrogen through the solution for 20 min. The reactor was immersed in a cooling bath at –25 °C, and a stream of MeOH at –15 °C was circulated through the refrigeration jacket. The mixture was irradiated using a medium pressure 400 W mercury lamp (400 W MP mercury lamp 3040, photochemical reactors ltd.) for 7 h. The progress of the reaction was monitored by GC. Then, the reaction mixture was concentrated under reduced pressure, the residue was dissolved in hexane/EtOAc (1:1), and the crude material was passed through a silica gel pad. Evaporation of the solvent under reduced pressure gave a diastereomeric mixture of the dichlorocyclobutane derivatives, which was used in the following step without further purification.

The mixture was split into three portions, each one was dissolved in EtOH (80% aq.; 4 mL), and activated Zn dust (3.6 g, 55 mmol) was added. Each mixture was irradiated under pressure in a focussed microwave reactor at 100 °C for 15 min. After cooling, the reaction mixtures were combined, and the crude material was filtered through Celite. The solid was washed several times with EtOH and EtOAc. The filtrate was evaporated to give a residue, which was subjected to column chromatography (hexane/EtOAc, 6:1) to give **16** (1.16 g, 5.17 mmol, 56%) as a colourless oil. $[\alpha]_D$ = –211.9 ($c$ = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2975, 2874, 1768, 1734, 1484, 1284 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 6.35 (ddd, $^3J_{H,H}$ = 2.7, 0.7, $^4J_{H,H}$ = 0.5 Hz, 1 H, 6-H), 6.30 (dd, $^3J_{H,H}$ = 2.7, 0.8 Hz, 1 H, 7-H), 4.60 (dddd, $^3J_{H,H}$ = 3.0, 2.8, 1.5, $^4J_{H,H}$ = 0.5 Hz, 1 H, 4-H), 4.26 (dd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 2.8 Hz, 1 H, 8-H), 4.12 (dd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 3.0 Hz, 1 H, 8-H), 3.70 (dd, $^3J_{H,H}$ = 3.5, 0.8 Hz, 1 H, 1-H), 3.45 (ddd, $^3J_{H,H}$ = 3.5, 1.5, 0.7 Hz, 1 H, 5-H), 1.20 [s, 9 H, $(CH_3)_3C$] ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$): $\delta$ = 178.0 (C=O), 174.6 (C=O), 140.7 (CH, C-6/C-7), 139.2 (CH, C-6/C-7), 76.2 (CH, C-4), 65.7 ($CH_2$, C-8), 47.6 (CH, C-1), 44.2 (CH, C-5), 38.6 [C, $(CH_3)_3C$], 27.1 [$CH_3$, $(CH_3)_3C$] ppm. $C_{12}H_{16}O_4$ (224.26): calcd. C 64.27, H 7.19; found C 64.14, H 7.13.

**(1*S*)-1-[(1*S*,4*R*)-4-(Hydroxymethyl)-2-cyclobutenyl]ethane-1,2-diol (20):** $LiBH_4$ (2.0 M solution in THF; 5 mL, 10.00 mmol) was added dropwise to a solution of **16** (462 mg, 2.06 mmol) in dry THF (34 mL) under an argon atmosphere. The mixture was heated to 90 °C and stirred at that temperature for 4 h. Then the reaction mixture was cooled to room temp., and it was quenched by adding $Na_2SO_4{\cdot}10H_2O$ until no further bubbling was observed. The suspension was stirred overnight, then it was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (from hexane/EtOAc, 1:1, to $CH_2Cl_2$/MeOH, 9:1) to give **20** (252 mg, 1.74 mmol, 75%) as a colourless oil. $[\alpha]_D$ = +22.7 ($c$ = 1.5, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3293 (br), 2885, 1648, 1427, 1288, 1152, 1087 $cm^{-1}$. $^1H$ NMR (360 MHz, $CDCl_3$): $\delta$ = 6.04 (dd, $^3J_{H,H}$ = 2.9, 0.8 Hz, 1 H, 2′-H), 6.02 (dd, $^3J_{H,H}$ = 2.9, 0.8 Hz, 1 H, 3′-H), 4.65 (br. s, 1 H, OH), 4.05 (br. s, 1 H, OH), 3.80 (m, 4 H, 2 1′′-H, 1-H, 2-H), 3.53 (dd, $^2J_{H,H}$ = 11.3, $^3J_{H,H}$ = 6.9 Hz, 1 H, 2-H), 3.25 (dddd, $^3J_{H,H}$ = 11.5, 4.0, 4.0, 0.8 Hz, 1 H, 4′-H), 3.02 (ddd, $^3J_{H,H}$ = 10.6, 4.0, 0.8 Hz, 1 H, 1′-H), 2.18 (br. s, 1 H, OH) ppm. $^{13}C$ NMR (90 MHz, $CDCl_3$): $\delta$ = 137.8 (CH, C-2′/C-3′), 137.2 (CH, C-2′/C-3′), 72.3 (CH, C-1), 65.1 ($CH_2$, C-2), 62.4 ($CH_2$, C-1′′), 48.6 (CH, C-1′/C-4′), 48.1 (CH, C-1′/C-4′) ppm. HRMS ($ESI^+$): calcd. for $[C_7H_{12}O_3 + Na]^+$ 167.0679; found 167.0676.

**{(1*R*,4*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]cyclobut-2-en-1-yl}methanol (17):** Anhydrous sodium sulfate (6.70 g, 47.20 mmol), anhydrous copper sulfate (2.50 g, 15.68 mmol), and HCl (concentrated; one drop) were added to a stirred solution of triol **20** (240 mg, 1.66 mmol) in acetone (36 mL) under an argon atmosphere. The reaction mixture was stirred for 4 d at room temp., then the reaction was quenched by the slow addition of $NH_3$ (30% aq.), and the crude mixture was filtered through a pad of Celite. The solvent was evaporated under reduced pressure without heating (because the product was volatile), and the residue was purified by column chromatography over alumina (from hexane/diethyl ether, 3:1, to diethyl ether) to give **17** (261 mg, 1.41 mmol, 85%) as a colourless oil. $[\alpha]_D$ = +16.3 ($c$ = 0.98, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3452 (br), 1370, 1212, 1150, 1058, 1019, 846, 745 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 6.09 (dd, $^3J_{H,H}$ = 2.9, 1.1 Hz, 1 H, 2′-H), 5.93 (ddd, $^3J_{H,H}$ = 2.9, 0.9, $^4J_{H,H}$ = 0.4 Hz, 1 H, 3′-H), 4.18 (ddd, $^3J_{H,H}$ = 10.4, 6.0, 6.0 Hz, 1 H, 4′′-H), 4.11 (dd, $^2J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.0 Hz, 1 H, 5′′-H), 3.71 (m, 3 H, 2 1-H, 5′′-H), 3.45 (dd, $^3J_{H,H}$ = 9.1, 4.1 Hz, 1 H, OH), 3.26 (m, 1 H, 1′-H), 3.02 (ddd, $^3J_{H,H}$ = 10.4, 4.1, 0.9 Hz, 1 H, 4′-H), 1.43 (s, 3 H, C$H_3$-C-2′′), 1.37 (s, 3 H, C$H_3$-C-2′′) ppm. $^{13}C$ NMR (62.5 MHz, $CDCl_3$): $\delta$ = 138.9 (CH, C-2′), 136.0 (CH, C-3′), 109.5 (C, C-2′′), 75.9 (CH, C-4′′), 68.5 ($CH_2$, C-5′′), 62.0 ($CH_2$, C-1), 49.1 (CH, C-1′/C-4′), 48.8 (CH, C-1′/C-4′), 26.9 ($CH_3$, $CH_3$-C-2′′), 25.6 ($CH_3$, $CH_3$-C-2′′) ppm. HRMS ($ESI^+$): calcd. for $[C_{10}H_{16}O_3 + Na]^+$ 207.0992; found 207.0995.

**3-Benzoyl-1-({(1*R*,2*S*,3*S*)-3-*tert*-butyldiphenylsilyloxy-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)thymine (21):** Di-*tert*-butyl azodicarboxylate (203 mg, 0.88 mmol) was added to a solution of $PPh_3$ (243 mg, 0.88 mmol) in dry THF (5.5 mL), and the solution was stirred at room temp. for 30 min. Then a suspension of **14** (193 mg, 0.44 mmol) and *N*3-benzoylthymine (202 mg, 0.88 mmol) in dry THF (5.5 mL) was added to the original solution, and the resulting mixture was heated at reflux. After 2 h, the mixture was cooled to room temp. The solvent was evaporated, and the residue was purified by column chromatography (hexane/diethyl ether, 2:1 to 1:1) to give **21** (208 mg, 0.32 mmol, 73%) as a white foam. $[\alpha]_D$ = +37.0 ($c$ = 0.87, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2931, 1746, 1698, 1653, 1429, 1368, 1239, 1154, 1109 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.90–7.84 (m, 2 H, Ar), 7.65–7.54 (m, 5 H, Ar), 7.49–7.32 (m, 9 H, Ar, 6-H), 4.67 (ddd, $^3J_{H,H}$ = 10.8, 6.8, 6.8 Hz, 1 H, 4′′′-H), 4.39 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.5 Hz, 1 H, 5′′′-H), 4.18 (ddd, $^3J_{H,H}$ = 7.5, 7.5, 7.5 Hz, 1 H, 3′′-H), 3.95 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 6.8 Hz, 1 H, 1′-H), 3.82 (dd, $^2J_{H,H}$ = 14.2,

$^3J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 3.67 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.8 Hz, 1 H, 5′′′-H), 2.66 (dddd, $^3J_{H,H}$ = 10.8, 7.5, 7.5, 3.4 Hz, 1 H, 2′′H), 2.19–2.07 (m, 1 H, 1′′-H), 2.00–1.86 (m, 2 H, 4′′-H), 1.91 (d, $^4J_{H,H}$ = 1.0 Hz, 3 H, C$H_3$-C-5), 1.42 (s, 3 H, C$H_3$-C-2′′′), 1.40 (s, 3 H, C$H_3$-C-2′′′), 1.04 [s, 9 H, (C$H_3$)$_3$C] ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 169.2 (C=O, Bz), 163.3 (C=O, C-4), 150.1 (C=O, C-2), 141.1 (CH, C-6), 135.7 (2 CH, Ph), 135.5 (2 CH, Ph), 134.9 (C, Bz), 133.5 (C, Ph), 133.1 (C, Ph), 131.9 (CH, Bz), 130.4 (2 CH, Bz), 130.1 (CH, Ph), 130.0 (CH, Ph), 129.2 (2 CH, Bz), 127.9 (2 CH, Ph), 127.8 (2 CH, Ph), 109.7 (C, C-5), 108.2 (C, C-2′′′), 73.0 (CH, C-4′′′), 70.4 ($CH_2$, C-5′′′), 64.8 (CH, C-3′′), 50.0 (CH, C-2′′), 49.9 ($CH_2$, C-1′), 36.5 ($CH_2$, C-4′′), 28.7 (CH, C-1′′), 27.0 [4 $CH_3$, (C$H_3$)$_3$C/C$H_3$-C-2′′′], 25.7 ($CH_3$, C$H_3$-C-2′′′), 19.0 [C, (C$H_3$)$_3$C), 12.4 ($CH_3$, C$H_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{38}H_{44}N_2O_6Si$ + Na]$^+$ 675.2861; found 675.2860.

**3-Benzoyl-1-({(1*R*,2*S*,3*S*)-3-{[*tert*-butyl(diphenyl)silyl]oxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-5-fluoro-thymine (22):** DBAD (85 mg, 0.37 mmol) was added to a solution of $PPh_3$ (97 mg, 0.37 mmol) in dry THF (2.5 mL), and the solution was stirred at room temp. for 30 min. Then, a suspension of **14** (82 mg, 0.19 mmol) and *N*3-benzoyl-5-fluorouracil (87 mg, 0.37 mmol) in dry THF (2.5 mL) was added to the original solution, and the resulting mixture was heated at reflux. After 5 h, the mixture was cooled to room temp. The solvent was evaporated, and the residue was purified by column chromatography (hexane/diethyl ether, 5:1 to 1:1) to give **22** (76 mg, 0.12 mmol, 62%) as a white foam. $[\alpha]_D$ = +43.7 (*c* = 0.93, $CHCl_3$). IR (ATR): ṽ = 2929, 1751, 1712, 1666, 1449, 1237, 1156 cm$^{-1}$. $^1$H NMR (250 MHz, $CDCl_3$): δ = 7.91–7.79 (m, 2 H, Ar), 7.83 (d, $^3J_{F,H}$ = 6.1 Hz, 1 H, 6-H), 7.69–7.52 (m, 5 H, Ar), 7.52–7.30 (m, 8 H, Ar), 4.67 (ddd, $^3J_{H,H}$ = 10.9, 6.5, 6.5 Hz, 1 H, 4′′′-H), 4.42 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 6.5 Hz, 1 H, 5′′′-H), 4.18 (ddd, $^3J_{H,H}$ = 7.5, 7.5, 7.5 Hz, 1 H, 3′′-H), 3.97 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.2 Hz, 1 H, 1′-H), 3.75 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 7.4 Hz, 1 H, 1′-H), 3.71 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 6.5 Hz, 1 H, 5′′′-H), 2.69 (dddd, $^3J_{H,H}$ = 10.9, 7.5, 7.5, $^4J_{H,H}$ = 3.7 Hz, 1 H, 2′′H), 2.18–2.02 (m, 1 H, 1′′-H), 1.99–1.79 (m, 2 H, 4′′-H), 1.43 (s, 6 H, 2 C$H_3$-C-2′′′), 1.05 [s, 9 H, (C$H_3$)$_3$C] ppm. $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ = 167.5 (s, C=O, Bz), 156.4 (d, $J_{C,F}$ = 27.0 Hz, C=O, C-4), 148.6 (s, C=O, C-2), 139.5 (d, $J_{C,F}$ = 237.3 Hz, C, C-5), 135.7 (s, 2 CH, Ph), 135.5 (s, 2 CH, Ph), 135.4 (s, C, Bz), 133.4 (s, C, Ph), 133.0 (s, C, Ph), 131.3 (s, CH, Bz), 130.6 (s, 2 CH, Bz), 130.2 (s, CH, Ph), 130.1 (s, CH, Ph), 129.8 (d, $J_{C,F}$ = 33.5 Hz, CH, C-6), 129.3 (s, 2 CH, Bz), 128.0 (s, 2 CH, Ph), 127.9 (s, 2 CH, Ph), 108.5 (s, C, C-2′′′), 72.9 (s, CH, C-4′′′), 70.4 (s, $CH_2$, C-5′′′), 64.7 (s, CH, C-3′′), 50.1 (s, $CH_2$, C-1′), 50.0 (s, CH, C-2′′), 36.3 (s, $CH_2$, C-4′′), 28.5 (s, CH, C-1′′), 27.0 [s, 3 $CH_3$, (C$H_3$)$_3$C], 26.9 (s, $CH_3$, C$H_3$-C-2′′′), 25.7 (s, $CH_3$, C$H_3$-C-2′′′), 19.0 [s, C, (C$H_3$)$_3$C] ppm. $^{19}$F NMR (235 MHz, $CDCl_3$): δ = –167.3 (d, $J_{F,6}$ = 6.1 Hz) ppm. HRMS (ESI$^+$): calcd. for [$C_{37}H_{41}FN_2O_6Si$ + Na]$^+$ 679.2610; found 679.2616.

**1-({(1*R*,2*S*,3*S*)-3-(*tert*-Butyldiphenylsilyloxy)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)thymine (23):** Compound **21** (116 mg, 0.18 mmol) was dissolved in $MeNH_2$ (33% solution in EtOH; 3 mL). The solution was stirred for 30 min at room temp. Then the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **23** (78 mg, 0.14 mmol, 80%) as a white foam. $[\alpha]_D$ = +40.6 (*c* = 0.42, $CHCl_3$). IR (ATR): ṽ = 2930, 2857, 1672, 1462, 1427, 1369, 1154, 1107 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ = 8.97 (br. s, 1 H, NH), 7.61–7.55 (m, 4 H, Ph), 7.47–7.33 (m, 6 H, Ph), 7.23 (q, $^4J_{H,H}$ = 1.0 Hz, 1 H, 6-H), 4.67 (ddd, $^3J_{H,H}$ = 10.8, 6.5, 6.5 Hz, 1 H, 4′′′-H), 4.39 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.5 Hz, 1 H, 5′′′-H), 4.17 (ddd, $^3J_{H,H}$ = 7.3, 7.3, 7.3 Hz, 1 H, 3′′-H), 3.89 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 3.78 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 6.8 Hz, 1 H, 1′-H), 3.65 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.5 Hz, 1 H, 5′′′-H), 2.63 (dddd, $^3J_{H,H}$ = 10.8, 7.3, 7.3, $^4J_{H,H}$ = 3.6 Hz, 1 H, 2′′-H), 2.17–2.06 (m, 1 H, 1′′-H), 2.00–1.88 (m, 2 H, 4′′-H), 1.87 (d, $^4J_{H,H}$ = 1.0 Hz, 3 H, C$H_3$-C-5), 1.41 (s, 3 H, C$H_3$-C-2′′′), 1.38 (s, 3 H, C$H_3$-C-2′′′), 1.05 [s, 9 H, (C$H_3$)$_3$C] ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 164.5 (C=O, C-4), 151.1 (C=O, C-2), 141.5 (CH, C-6), 135.8 (2 CH, Ph), 135.5 (2 CH, Ph), 133.5 (C, Ph), 133.2 (C, Ph), 130.1 (CH, Ph), 130.0 (CH, Ph), 127.9 (2 CH, Ph), 127.8 (2 CH, Ph), 109.7 (C, C-5), 108.2 (C, C-2′′′), 73.0 (CH, C-4′′′), 70.4 ($CH_2$, C-5′′′), 64.8 (CH, C-3′′), 49.9 (CH, C-2′′), 49.8 ($CH_2$, C-1′), 36.5 ($CH_2$, C-4′′), 28.6 (CH, C-1′′), 27.0 [3 $CH_3$, (C$H_3$)$_3$C], 27.0 ($CH_3$, C$H_3$-C-2′′′), 25.7 ($CH_3$, C$H_3$-C-2′′′), 19.0 [C, (C$H_3$)$_3$C], 12.4 ($CH_3$, C$H_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{31}H_{40}N_2O_5Si$ + Na]$^+$ 571.2599; found 571.2602.

**1-({(1*R*,2*R*,3*S*)-2-[(1*S*)-1,2-Dihydroxyethyl]-3-hydroxycyclobutyl}-methyl)thymine (7-T):** Compound **23** (77 mg, 0.14 mmol) was dissolved in MeOH (5 mL), and *p*-toluenesulfonic acid (27 mg, 0.14 mmol) was added. The solution was heated at reflux for 5 h. The solution was cooled to room temperature, and the solvent was evaporated. The residue was purified by filtration through DOWEX 1X8 resin followed by column chromatography (from EtOAc to EtOAc/MeOH, 9:1) to give **7-T** (32 mg, 0.12 mmol, 84%) as a white solid, m.p. 45–47 °C (MeOH). $[\alpha]_D$ = –49.1 (*c* = 1.06, MeOH). IR (ATR): ṽ = 3100–3500, 2963, 1655, 1260 cm$^{-1}$. $^1$H NMR (400 MHz, [D$_4$]methanol): δ = 7.48 (d, $^4J_{H,H}$ = 1.2 Hz, 1 H, 6-H), 4.24 (ddd, $^3J_{H,H}$ = 6.5, 6.5, 6.5 Hz, 1 H, 3′′-H), 4.15 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 5.2 Hz, 1 H, 1′-H), 4.12–4.15 (m, 1 H, 1′′′-H), 4.05 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 10.4 Hz, 1 H, 1′-H), 3.78 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 3.7 Hz, 1 H, 2′′′-H), 3.46 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 6.4 Hz, 1 H, 2′′′-H), 2.65–2.55 (m, 1 H, 2′′-H), 2.55–2.45 (m, 1 H, 1′′-H), 2.33 (dddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 6.5, 6.5, $^4J_{H,H}$ = 2.5 Hz, 1 H, 4′′-H), 1.90 (ddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 7.8, 6.5 Hz, 1 H, 4′′-H), 1.86 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, C$H_3$-C-5) ppm. $^{13}$C NMR (100 MHz, [D$_4$]methanol): δ = 166.9 (C=O, C-4), 153.1 (C=O, C-2), 143.6 (CH, C-6), 110.7 (C, C-5), 70.1 (CH, C-1′′′), 67.1 ($CH_2$, C-2′′′), 66.1 (CH, C-3′′), 51.7 ($CH_2$, C-1′), 46.9 (CH, C-2′′), 35.2 ($CH_2$, C-4′′), 31.4 (CH, C-1′′), 12.2 ($CH_3$, C$H_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{12}H_{18}N_2O_5$ + Na]$^+$ 293.1108; found 293.1106.

**1-({(1*R*,2*S*,3*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-5-fluoro-thymine (24):** Compound **22** (78 mg, 0.12 mmol) was dissolved in $MeNH_2$ (33% solution in EtOH; 2.5 mL). The solution was stirred for 30 min at room temp. Afterwards, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/EtOAc, 1:1) to give **24** (63 mg, 0.11 mmol, 95%) as a yellow foam. $[\alpha]_D$ = +52.0 (*c* = 1.23, $CHCl_3$). IR (ATR): ṽ = 3070, 2931, 2857, 1688, 1662, 1372, 1238, 1155, 1109 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.47 (d, $^4J_{F,H}$ = 5.2 Hz, 1 H, N*H*), 7.70 (d, $^3J_{F,H}$ = 5.2 Hz, 1 H, 6-H), 7.60–7.55 (m, 4 H, Ph), 7.47–7.34 (m, 6 H, Ph), 4.66 (ddd, $^3J_{H,H}$ = 10.9, 6.5, 6.5 Hz, 1 H, 4′′′-H), 4.41 (dd, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 6.5 Hz, 1 H, 5′′′-H), 4.18 (ddd, $^3J_{H,H}$ = 8.5, 7.3, 7.3 Hz, 1 H, 3′′-H), 3.92 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.5 Hz, 1 H, 1′-H), 3.71 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 8.0 Hz, 1 H, 1′-H), 3.69 (dd, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 6.5 Hz, 1 H, 5′′′-H), 2.65 (dddd, $^3J_{H,H}$ = 10.9, 7.3, 7.3, $^4J_{H,H}$ = 3.7 Hz, 1 H, 2′′-H), 2.16–2.04 (m, 1 H, 1′′-H), 1.97 (dddd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 7.3, 7.3, $^4J_{H,H}$ = 3.7 Hz, 1 H, 4′′-H), 1.87 (ddd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 10.8, 8.5 Hz, 1 H, 4′′-H), 1.42 (s, 3 H, C$H_3$-C-2′′′), 1.40 (s, 3 H, C$H_3$-C-2′′′), 1.05 [s, 9 H, (C$H_3$)$_3$C] ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 157.4 (d, $J_{C,F}$ = 26.0 Hz, C=O, C-4), 149.8 (s, C=O, C-2), 139.9 (d, $J_{C,F}$ = 235.5 Hz, C, C-5), 135.7 (s, 2 CH, Ph), 135.5 (s, 2 CH, Ph), 133.4

(s, C, Ph), 133.0 (s, C, Ph), 130.2 (s, CH, Ph), 130.1 (s, CH, Ph), 129.9 (d, $J_{C,F}$ = 31.5 Hz, CH, C-6), 128.0 (s, 2 CH, Ph), 127.9 (s, 2 CH, Ph), 108.4 (s, C, C-2′′′), 72.8 (s, CH, C-4′′′), 70.4 (s, $CH_2$, C-5′′′), 64.7 (s, CH, C-3′′), 49.9 (s, $CH_2$, C-1′), 49.9 (s, CH, C-2′′), 36.3 (s, $CH_2$, C-4′′), 28.4 (s, CH, C-1′′), 27.0 [s, 3 $CH_3$, $(CH_3)_3C$], 26.8 (s, $CH_3$, $CH_3$-C-2′′′), 25.7 (s, $CH_3$, $CH_3$-C-2′′′), 19.0 [s, C, $(CH_3)_3C$] ppm. $^{19}F$ NMR (376 MHz, $CDCl_3$): $\delta$ = –167.7 (t, $J_{F,NH}$ = 5.2, $J_{F,6}$ = 5.2 Hz) ppm. HRMS (ESI$^+$): calcd. for $[C_{30}H_{37}FN_2O_5Si + Na]^+$ 575.2348; found 575.2353.

**1-({(1*R*,2*R*,3*S*)-2-[(1*S*)-1,2-Dihydroxyethyl]-3-hydroxycyclobutyl}methyl)-5-fluoro-thymine (7-U$^F$):** Compound **24** (62 mg, 0.11 mmol) was dissolved in MeOH (4 mL), and *p*-toluenesulfonic acid (21 mg, 0.11 mmol) was added. The solution was heated at reflux overnight. The solution was cooled to room temp., and the solvent was evaporated. The residue was purified by filtration through DOWEX 1X8 resin followed by column chromatography (from EtOAc to EtOAc/MeOH, 9:1) to give **7-U$^F$** (20 mg, 0.07 mmol, 67%) as a yellow oil. $[\alpha]_D$ = –36.2 (*c* = 0.85, MeOH). IR (ATR): $\tilde{\nu}$ = 3500–3100, 2939, 1657, 1371, 1237 cm$^{-1}$. $^1H$ NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.89 (d, $^3J_{F,H}$ = 6.3 Hz, 1 H, 6-H), 4.23 (ddd, $^3J_{H,H}$ = 6.6, 6.6, 6.6 Hz, 1 H, 3′′-H), 4.13 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 5.6 Hz, 1 H, 1′-H), 4.14–4.07 (m, 1 H, 1′′′-H), 4.03 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 9.8 Hz, 1 H, 1′-H), 3.78 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 3.7 Hz, 1 H, 2′′′-H), 3.45 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 6.3 Hz, 1 H, 2′′′-H), 2.59 (dddd, $^3J_{H,H}$ = 11.0, 8.8, 6.6, $^4J_{H,H}$ = 2.4 Hz, 1 H, 2′′-H), 2.55–2.45 (m, 1 H, 1′′-H), 2.37 (dddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 6.6, 6.6, $^4J_{H,H}$ = 2.4 Hz, 1 H, 4′′-H), 1.89 (ddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 8.4, 6.6 Hz, 1 H, 4′′-H) ppm. $^{13}C$ NMR (100 MHz, [D$_4$]methanol): $\delta$ = 159.9 (d, $J_{C,F}$ = 25.7 Hz, C=O, C-4), 151.6 (s, C=O, C-2), 141.4 (d, $J_{C,F}$ = 231.5 Hz, C, C-5), 131.6 (d, $J_{C,F}$ = 33.1 Hz, CH, C-6), 70.0 (s, CH, C-1′′′), 67.2 (s, $CH_2$, C-2′′′), 65.9 (s, CH, C-3′′), 52.0 (s, $CH_2$, C-1′), 47.0 (s, CH, C-2′′), 35.2 (s, $CH_2$, C-4′′), 31.1 (s, CH, C-1′′) ppm. $^{19}F$ NMR (376 MHz, [D$_4$]methanol): $\delta$ = –171.0 (d, $J_{F,6}$ = 6.3 Hz) ppm. HRMS (ESI$^+$): calcd. for $[C_{11}H_{15}FN_2O_5 + Na]^+$ 297.0857; found 297.0854.

**1-[4-Hydroxy-2-(2-hydroxyethyl)butyl]thymine (25-T):** Compound **7-T** (25 mg, 0.09 mmol) was dissolved in THF/$H_2O$ (1:1; 2 mL). The solution was cooled to 0 °C in an ice bath, and $NaIO_4$ (26 mg, 0.12 mmol) was added. After 15 min, the bath was removed, and the mixture was stirred at room temp. After 30 min, THF (2 mL) was added, and the solution was cooled to 0 °C. The white precipitate formed was filtered off and the filtrate was cooled to 0 °C. Then, $NaBH_4$ (17 mg, 0.44 mmol) was added, and the reaction mixture was stirred for 2 h. After this time, it was quenched by the addition of $NH_4Cl$ (saturated aq.). When the bubbling ceased, some drops of concentrated $NH_3$ were added, and the mixture was evaporated to dryness. The residue was purified by column chromatography (from EtOAc to EtOAc/MeOH, 9:1) to give **25-T** (16 mg, 0.07 mmol, 73%) as a white solid, m.p. 96–98 °C (MeOH). IR (ATR): $\tilde{\nu}$ = 3461, 3354, 2915, 1668, 1470, 1420, 1348, 1226, 1102, 1075 cm$^{-1}$. $^1H$ NMR (360 MHz, [D$_4$]methanol): $\delta$ = 7.45 (q, $^4J_{H,H}$ = 1.2 Hz, 1 H, 6-H), 3.71 (d, $^3J_{H,H}$ = 10.5 Hz, 2 H, 1′-H), 3.69–3.57 (m, 4 H, 4′-H), 2.10 (dq, $^3J_{H,H}$ = 10.5, 6.7 Hz, 1 H, 2′-H), 1.88 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, C$H_3$-C-5), 1.56 (m, 4 H, 3′-H) ppm. $^{13}C$ NMR (90 MHz, [D$_4$]methanol): $\delta$ = 166.9 (C=O, C-4), 153.3 (C=O, C-2), 143.5 (CH, C-6), 111.0 (C, C-5), 60.4 (2 $CH_2$, C-4′), 53.1 ($CH_2$, C-1′), 35.1 (2 $CH_2$, C-3′), 33.3 (CH, C-2′), 12.2 ($CH_3$, $CH_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for $[C_{11}H_{18}N_2O_4 + Na]^+$ 265.1159; found 265.1159.

**1-({(1*R*,2*R*,3*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-hydroxycyclobutyl}methyl)thymine (26):** TBAF (1 M solution in THF; 630 µL, 0.63 mmol) was added to a solution of **23** (205 mg, 0.31 mmol) in THF (5.5 mL). After 2 h, the mixture was evaporated to dryness, and the residue was purified by column chromatography (from hexane/EtOAc, 1:1, to EtOAc) to give a residue. This material was dissolved in $MeNH_2$ (33% solution in EtOH; 6.5 mL). The solution was stirred for 2 h at room temp. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (from hexane/EtOAc, 1:1, to EtOAc) to give **26** (96 mg, 0.31 mmol, 99%) as a white foam. $^1H$ NMR (250 MHz, $CDCl_3$): $\delta$ = 9.38–9.25 (m, 1 H, NH), 7.25 (q, $^4J_{H,H}$ = 0.9 Hz, 1 H, 6-H), 4.58 (ddd, $^3J_{H,H}$ = 10.6, 6.8, 6.6 Hz, 1 H, 4′′′-H), 4.32–4.19 (m, 2 H, 5′′′-H, 3′′-H), 4.02 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 7.3 Hz, 1 H, 1′-H), 3.81 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 6.5 Hz, 1 H, 1′-H), 3.60 (dd, $^2J_{H,H}$ = 8.2, $^3J_{H,H}$ = 7.2 Hz, 1 H, 5′′′-H), 2.65 (dddd, $^3J_{H,H}$ = 10.6, 7.2, 7.2, $^4J_{H,H}$ = 3.6 Hz, 1 H, 2′′-H), 2.52–2.26 (m, 3 H, 1′′-H, 4′′-H, OH), 1.97 (dddd, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 8.6, 8.6 Hz, 1 H, 4′′-H), 1.88 (d, $^4J_{H,H}$ = 0.9 Hz, 3 H, C$H_3$-C-5), 1.39 (s, 3 H, C$H_3$-C-2′′′), 1.37 (s, 3 H, C$H_3$-C-2′′′) ppm.

**1-({(1*R*,2*R*,3*S*)-3-(Benzyloxy)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)thymine (27):** A suspension of *t*BuOK (111 mg, 0.94 mmol) in dry THF (3 mL) was stirred for 15 min at room temp. Then a solution of **26** (97 mg, 0.31 mmol) in dry THF (3 mL) was added dropwise to the *t*BuOK suspension. The mixture was stirred for 30 min at room temp. At the same time, BnBr (114 µL, 0.94 mmol) was added dropwise to a suspension of NaI (142 mg, 0.94 mmol) in dry THF (2 mL), and the mixture was stirred for 30 min at room temp. At this point, the BnI solution was added dropwise to the original solution, and the resulting mixture was stirred for 30 min. The reaction was quenched by the addition of $NH_4Cl$ (saturated aq.). The crude mixture was diluted with EtOAc, and the phases were separated. The aqueous phase was extracted with EtOAc, and the organic extracts were washed with $NaHCO_3$ (saturated aq.) and brine. The organic phase was then dried with $MgSO_4$, and the solvents were evaporated to dryness. Purification of the residue by column chromatography (hexane/EtOAc, 1:1) gave **27** (97 mg, 0.24 mmol, 78%) as a white solid, m.p. 156–158 °C (hexane/EtOAc). $[\alpha]_D$ = +52.4 (*c* = 0.96, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3205, 2930, 1681, 1456, 1373, 1323, 1255, 1158, 1111, 1050 cm$^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 7.99 (br. s, 1 H, N*H*), 7.36–7.24 (m, 6 H, 6-H, Ph), 4.58 (ddd, $^3J_{H,H}$ = 10.7, 6.8, 6.8 Hz, 1 H, 4′′′-H), 4.43 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, C$H_2$-Ph), 4.31 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, C$H_2$-Ph), 4.27 (dd, $^2J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.8 Hz, 1 H, 5′′′-H), 3.97 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 6.8 Hz, 1 H, 1′-H), 3.95 (ddd, $^3J_{H,H}$ = 7.1, 7.1, 7.1 Hz, 1 H, 3′′-H), 3.85 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 6.8 Hz, 1 H, 1′-H), 3.61 (dd, $^2J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.8 Hz, 1 H, 5′′′-H), 2.72 (dddd, $^3J_{H,H}$ = 10.7, 7.4, 7.1, $^4J_{H,H}$ = 3.2 Hz, 1 H, 2′′-H), 2.47–2.32 (m, 2 H, 1′′-H, 4′′-H), 1.98–1.89 (m, 1 H, 4′′-H), 1.90 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, C$H_3$-C-5), 1.38 (s, 6 H, 2 C$H_3$-C-2′′′) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 164.0 (C=O, C-4), 151.0 (C=O, C-2), 141.5 (CH, C-6), 138.1 (C, Ph), 128.6 (2 CH, Ph), 127.9 (CH, Ph), 127.5 (2 CH, Ph), 109.8 (C, C-5), 108.4 (C, C-2′′′), 72.9 (CH, C-4′′′), 70.6 ($CH_2$, $CH_2$-Ph), 70.2 ($CH_2$, C-5′′′), 69.6 (CH, C-3′′), 50.1 ($CH_2$, C-1′), 48.3 (CH, C-2′′), 33.5 ($CH_2$, C-4′′), 29.1 (CH, C-1′′), 27.1 ($CH_3$, $CH_3$-C-2′′′), 25.8 ($CH_3$, $CH_3$-C-2′′′), 12.4 ($CH_3$, $CH_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for $[C_{22}H_{28}N_2O_5 + Na]^+$ 423.1890; found 423.1886.

**1-({(1*R*,2S,3*S*)-3-(Benzyloxy)-2-[(1*S*)-1,2-dihydroxyethyl]cyclobutyl}methyl)thymine (28):** Compound **27** (78 mg, 0.19 mmol) was dissolved in MeOH (8 mL), and *p*-toluenesulfonic acid (36 mg, 0.19 mmol) was added. The solution was stirred for 4 h at room temp., then the reaction mixture was passed through DOWEX 1X8 resin, concentrated under reduced pressure, and purified by column chromatography (from EtOAc to EtOAc/MeOH, 9:1) to give **28** (63 mg, 0.17 mmol, 90%) as a white solid, m.p. 66–68 °C (MeOH).

$[a]_D$ = –36.4 (*c* = 1.21, MeOH). IR (ATR): ṽ = 3500–3100, 2923, 1660, 1454, 1347, 1209, 1139 cm$^{-1}$. $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.39 (q, $^4J_{H,H}$ = 1.0 Hz, 1 H, 6-H), 7.36–7.22 (m, 5 H, Ph), 4.52 (d, $^2J_{H,H}$ = 11.8 Hz, 1 H, C$H_2$-Ph), 4.31 (d, $^2J_{H,H}$ = 11.8 Hz, 1 H, C$H_2$-Ph), 4.19–4.10 (m, 3 H, 2 1′-H, 1′′′-H), 4.06 (ddd, $^3J_{H,H}$ = 11.8, 7.4, 2.6 Hz, 1 H, 3′′-H), 3.81 (dd, $^2J_{H,H}$ = 11.3, $^3J_{H,H}$ = 3.0 Hz, 1 H, 2′′′-H), 3.43 (dd, $^2J_{H,H}$ = 11.3, $^3J_{H,H}$ = 6.5 Hz, 1 H, 2′′′-H), 2.74 (ddddd, $^3J_{H,H}$ = 10.5, 7.4, 7.2, $^4J_{H,H}$ = 2.2, 1.2 Hz, 1 H, 2′′-H), 2.62–2.50 (m, 1 H, 1′′-H), 2.29–2.20 (m, 1 H, 4′′-H), 1.98 (dddd, $^2J_{H,H}$ = 7.5, $^3J_{H,H}$ = 6.3, 2.6, $^4J_{H,H}$ = 1.2 Hz, 1 H, 4′′-H), 1.85 (d, $^4J_{H,H}$ = 1.0 Hz, 1 H, 6-H) ppm. $^{13}$C NMR (100 MHz, [D$_4$]methanol): $\delta$ = 166.9 (C=O, C-4), 153.2 (C=O, C-2), 143.4 (CH, C-6), 139.7 (C, Ph), 129.4 (2 CH, Ph), 128.8 (2 CH, Ph), 128.6 (CH, Ph), 110.8 (C, C-5), 73.4 (CH, C-3′′), 71.1 (CH$_2$, *C*H$_2$-Ph), 69.9 (CH, C-1′′′), 67.0 (CH$_2$, C-2′′′), 51.4 (CH$_2$, C-1′), 45.2 (CH, C-2′′), 32.4 (CH, C-1′′), 32.2 (CH$_2$, C-4′′), 12.2 (CH$_3$, *C*H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{19}H_{24}N_2O_5$ + Na]$^+$ 383.1577; found 383.1585.

**1-{[(1*R*,2*S*,3*S*)-3-(Benzyloxy)-2-(hydroxymethyl)cyclobutyl]methyl}thymine (29):** Compound **28** (80 mg, 0.22 mmol) was dissolved in THF/H$_2$O (1:1; 9 mL). The solution was cooled to 0 °C in an ice bath, and NaIO$_4$ (59 mg, 0.28 mmol) was added. After 15 min, the bath was removed, and the mixture was stirred at room temp. After about 30 min, THF (4.5 mL) was added, and the solution was cooled to 0 °C. The white precipitate formed was filtered off, and the filtrate was cooled to 0 °C. NaBH$_4$ (41 mg, 1.08 mmol) was added, and the reaction mixture was stirred for 2 h, after which time the reaction was quenched by the addition of NH$_4$Cl (saturated aq.). When the bubbling ceased, some drops of concentrated NH$_3$ were added, the mixture was evaporated to dryness, and the residue was purified by column chromatography (from EtOAc to EtOAc/MeOH, 9:1) to give **29** (56 mg, 0.17 mmol, 77%) as a white foam. $[a]_D$ = –57.9 (*c* = 1.21, MeOH). IR (ATR): ṽ = 3500–3000, 2930, 2361, 1661, 1468, 1352, 1252, 1206 cm$^{-1}$. $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.47 (q, $^4J_{H,H}$ = 0.8 Hz, 1 H, 6-H), 7.34–7.23 (m, 5 H, Ph), 4.43 (s, 2 H, C$H_2$-Ph), 4.06 (ddd, $^3J_{H,H}$ = 7.3, 7.3, 7.3 Hz, 1 H, 3′′-H), 4.00–3.91 (m, 3 H, 2 1′′′-H, 1′-H), 3.85 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 9.1 Hz, 1 H, 1′-H), 2.86–2.74 (m, 1 H, 2′′-H), 2.45–2.35 (m, 1 H, 1′′-H), 2.35–2.25 (m, 1 H, 4′′-H), 2.00 (ddd, $^2J_{H,H}$ = 10.2, $^3J_{H,H}$ = 10.0, 7.5 Hz, 1 H, 4′′-H), 1.85 (d, $^4J_{H,H}$ = 0.8 Hz, 3 H, C$H_3$-C-5) ppm. $^{13}$C NMR (100 MHz, [D$_4$]-methanol): $\delta$ = 166.9 (C=O, C-4), 153.0 (C=O, C-2), 143.4 (CH, C-6), 139.6 (C, Ph), 129.4 (2 CH, Ph), 128.9 (2 CH, Ph), 128.7 (CH, Ph), 110.8 (C, C-5), 71.8 (CH$_2$/CH, *C*H$_2$-Ph/C-3′′), 59.0 (CH$_2$, C-1′′′), 50.3 (CH$_2$, C-1′), 45.6 (CH, C-2′′), 34.0 (CH$_2$, C-4′′), 30.0 (CH, C-1′′), 12.2 (CH$_3$, *C*H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{18}H_{22}N_2O_4$ + Na]$^+$ 353.1472; found 353.1470.

**1-{[(1R,2*S*,3*S*)-3-Hydroxy-2-(hydroxymethyl)cyclobutyl]methyl}thymine (11-T):** Pd/C (9 mg) was added to a solution of **29** (55 mg, 0.17 mmol) in MeOH (2 mL). The mixture was heated to reflux, and ammonium formate (129 mg, 2.04 mmol) was added in portions throughout the course of the reaction. After 6 h, the mixture was cooled to room temp. and filtered through a pad of Celite. Evaporation of the solvent gave **11-T** (39 mg, 0.16 mmol, 98%) as a white solid, m.p. 164–166 °C (MeOH). $[a]_D$ = –50.8 (*c* = 1.22, MeOH). IR (ATR): ṽ = 3500–3000, 2926, 1705, 1664, 1432, 1351, 1236, 1055 cm$^{-1}$. $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.48 (q, $^4J_{H,H}$ = 1.0 Hz, 1 H, 6-H), 4.26 (ddd, $^3J_{H,H}$ = 7.6, 7.6, 7.6 Hz, 1 H, 3′′-H), 3.97 (d, $^3J_{H,H}$ = 7.4 Hz, 2 H, 2 1′′′-H), 3.95 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 5.7 Hz, 1 H, 1′-H), 3.85 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 8.8 Hz, 1 H, 1′-H), 2.74–2.65 (m, 1 H, 2′′-H), 2.42–2.30 (m, 2 H, 1′′-H, 4′′-H), 2.01–1.90 (m, 1 H, 4′′-H), 1.86 (d, $^4J_{H,H}$ = 1.0 Hz, 3 H, C$H_3$-C-5) ppm. $^{13}$C NMR (100 MHz, [D$_4$]methanol): $\delta$ = 166.8 (C=O, C-4), 153.0 (C=O, C-2), 143.3 (CH, C-6), 110.9 (C, C-5), 65.2 (CH, C-3′′), 59.3 (CH$_2$, C-1′′′), 50.3 (CH$_2$, C-1′), 46.5 (CH, C-2′′), 36.1 (CH$_2$, C-4′′), 29.8 (CH, C-1′′), 12.2 (CH$_3$, *C*H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{11}H_{16}N_2O_4$ + Na]$^+$ 263.1002; found 263.1001. X-ray structure: diffraction-quality crystals of compound **11-T** were grown by slow evaporation from MeOH.

**3-Benzoyl-1-({(1*R*,4*S*)-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobut-2-en-1-yl}methyl)thymine (30):** A solution of DBAD (368 mg, 1.60 mmol) in anhydrous THF (4.5 mL) was added dropwise to a stirred suspension of alcohol **17** (147 mg, 0.80 mmol), *N3*-benzoylthymine (367 mg, 1.59 mmol), and triphenyl phosphine (421 mg, 1.60 mmol) in anhydrous THF (5.7 mL) under an argon atmosphere at 0 °C. The mixture was warmed to room temp. and stirred overnight. The organic solvent was removed under vacuum, and the resulting oil was purified by repeated column chromatography (hexane/EtOAc, 10:1 to 1:1) to give **30** (201 mg, 0.51 mmol, 63%) as a colourless oil. $[a]_D$ = +3.8 (*c* = 1.0, CHCl$_3$). IR (ATR): ṽ = 2984, 2930, 1745, 1696, 1648, 1436, 1238, 1062 cm$^{-1}$. $^1$H NMR (360 MHz, CDCl$_3$): $\delta$ = 7.91 (dd, *J* = 8.2, 1.2 Hz, 2 H, H-Bz), 7.63 (m, 1 H, H-Bz), 7.48 (t, *J* = 8.2 Hz, 2 H, H-Bz), 7.26 (q, $^4J_{H,H}$ = 1.1 Hz, 1 H, 6-H), 6.20 (dd, $^3J_{H,H}$ = 2.9, 0.9 Hz, 1 H, 2′′-H), 5.97 (d, $^3J_{H,H}$ = 2.9 Hz, 1 H, 3′′-H), 4.09 (m, 2 H, 5′′′-H, 4′′′-H), 3.99 (m, 2 H, 2 1′-H), 3.66 (m, 1 H, 5′′′-H), 3.33 (m, 1 H, 1′′-H), 3.07 (ddd, *J* = 9.8, 4.2, 0.8 Hz, 1 H, 4′′-H), 1.96 (d, $^4J_{H,H}$ = 1.1 Hz, 3 H, C$H_3$-C-5), 1.41 (s, 3 H, C$H_3$-C-2′′′), 1.35 (s, 3 H, C$H_3$-C-2′′′) ppm. $^{13}$C NMR (90 MHz, CDCl$_3$): $\delta$ = 169.2 (C=O, Bz), 163.3 (C=O, C-4), 150.1 (C=O, C-2), 140.8 (CH, C-6), 139.9 (CH, C-2′′), 136.4 (CH, C-3′′), 135.0 (CH, Bz), 131.9 (C, Bz), 130.5 (CH, Bz), 129.2 (CH, Bz), 110.4 (C, C-5), 109.7 (C, C-2′′′), 76.0 (CH, C-4′′′), 68.7 (CH$_2$, C-5′′′), 49.6 (CH, C-4′′), 49.0 (CH$_2$, C-1′), 45.0 (CH, C-1′′), 27.1 (CH$_3$, *C*H$_3$-C-2′′′), 25.8 (CH$_3$, *C*H$_3$-C-2′′′), 12.5 (CH$_3$, *C*H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{22}H_{24}N_2O_5$ + Na]$^+$ 419.1577; found 419.1585.

**3-Benzoyl-1-({(1*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]cyclobut-2-en-1-yl}methyl)thymine (31):** Compound **30** (52 mg, 0.13 mmol) was dissolved in MeOH (5.8 mL), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol) was added. The resulting mixture was stirred for 28 h at room temp. After removal of the solvent, the residue was purified by column chromatography (from hexane/EtOAc, 3:1, to EtOAc) to give **31** (30 mg, 0.08 mmol, 65%) as a colourless oil. $[a]_D$ = –28.0 (*c* = 1.1, CHCl$_3$). IR (ATR): ṽ = 3389 (br), 2923, 2853, 1741, 1691, 1639, 1259, 1021 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.90 (dd, *J* = 8.3, 1.0 Hz, 2 H, H-Bz), 7.63 (m, 1 H, H-Bz), 7.48 (t, *J* = 8.3 Hz, 2 H, H-Bz), 7.20 (d, $^4J_{H,H}$ = 0.8 Hz, 1 H, 6-H), 6.14 (d, $^3J_{H,H}$ = 2.7 Hz, 1 H, 2′′-H), 5.99 (d, $^3J_{H,H}$ = 2.7 Hz, 1 H, 3′′-H), 4.21 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.9 Hz, 1 H, 1′-H), 3.80 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 9.0 Hz, 1 H, 1′-H), 3.65 (m, 2 H, 2′′′-H, 1′′′-H), 3.41 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 7.2 Hz, 1 H, 2′′′-H), 3.28 (m, 1 H, 1′′-H), 2.98 (dd, *J* = 10.3, 4.1 Hz, 1 H, 4′′-H), 1.93 (d, $^4J_{H,H}$ = 0.8 Hz, 3 H, C$H_3$-C-5) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 169.4 (C=O, Bz), 163.3 (C=O, C-4), 150.4 (C=O, C-2), 140.7 (CH, C-6), 138.9 (CH, C-2′′), 137.2 (CH, C-3′′), 135.2 (CH, Bz), 131.7 (C, Bz), 130.5 (CH, Bz), 129.3 (CH, Bz), 110.9 (C, C-5), 72.1 (CH, C-1′′′), 65.6 (CH$_2$, C-2′′′), 49.1 (CH$_2$, C-1′), 48.5 (CH, C-4′′), 45.0 (CH, C-1′′), 12.5 (CH$_3$, *C*H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for [$C_{19}H_{20}N_2O_5$ + Na]$^+$ 379.1264; found 379.1264.

**1-({(1*R*,4*S*)-4-[(1*S*)-1,2-Dihydroxyethyl]cyclobut-2-en-1-yl}methyl)-thymine (8-T):** A solution of **31** (30 mg, 0.08 mmol) in MeNH$_2$ (33% solution in EtOH; 0.84 mL) was stirred overnight at room temp. The volatiles were removed under vacuum, and the residue was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH, 50:1 to 20:1, containing 0.5% NEt$_3$) to give thymine nucleoside

derivative **8-T** (18 mg, 0.07 mmol, 85%) as a white solid, m.p. 180–185 °C (MeOH). $[\alpha]_D$ = +249.9 ($c$ = 0.6, MeOH). IR (ATR): $\tilde{\nu}$ = 3362 (br), 2961, 1660, 1260, 1092, 1021 $cm^{-1}$. $^1H$ NMR (360 MHz, [D$_4$]methanol): $\delta$ = 7.46 (q, $^4J_{H,H}$ = 1.1 Hz, 1 H, 6-H), 6.17 (d, $^3J_{H,H}$ = 2.7 Hz, 1 H, 2′′-H), 6.12 (dd, $^3J_{H,H}$ = 2.7, 0.5 Hz, 1 H, 3′′-H), 4.19 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 5.1 Hz, 1 H, 1′-H), 3.84 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 10.6 Hz, 1 H, 1′-H), 3.65 (m, 2 H, 1′′′-H, 2′′′-H), 3.49 (dd, $^2J_{H,H}$ = 11.8, $^3J_{H,H}$ = 6.6 Hz, 1 H, 2′′′-H), 3.31 (m, 1 H, 1′′-H), 3.03 (ddd, $J$ = 9.7, 4.2, 0.5 Hz, 1 H, 4′′-H), 1.88 (d, $^4J_{H,H}$ = 1.1 Hz, 3 H, C$H_3$-C-5) ppm. $^{13}C$ NMR (90 MHz, [D$_4$]-methanol): $\delta$ = 166.9 (C=O, C-4), 153.1 (C=O, C-2), 143.5 (CH, C-6), 140.0 (CH, C-2′′), 138.4 (CH, C-3′′), 111.0 (C, C-5), 73.4 (CH, C-1′′′), 66.7 (CH$_2$, C-2′′′), 50.3 (CH$_2$, C-1′), 49.9 (CH, C-4′′), 46.2 (CH, C-1′′), 12.2 (CH$_3$, $C$H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for $[C_{12}H_{16}N_2O_4 + Na]^+$ 275.1002; found 275.0999.

**3-Benzoyl-1-({(1*R*,2*R*,3*S*,4*R*)-2,3-Dihydroxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobut-1-yl}methyl)thymine (32) and 3-Benzoyl-1-({(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobut-1-yl}methyl)thymine (33):** NMO (25 mg, 0.21 mmol) and $OsO_4$ (2.5 wt.-% in $t$BuOH solution; 54 μL, 4.31 μmol) were added to a stirred solution of **30** (34 mg, 0.09 mmol) in acetone/water (8:1; 0.9 mL). The reaction mixture was stirred for 6 h at room temp., then the reaction was quenched by the addition of $NaHSO_3$ (10% aq.; 0.9 mL), and the mixture was allowed to stir for 30 min. The aqueous phase was extracted with EtOAc (4× 2 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexane/EtOAc, 1:1 to 1:6) gave diol **32** (13 mg, 0.03 mmol, 35%) and its diastereomer **33** (12 mg, 0.03 mmol, 32%), both as white foams.

Data for **32**: $[\alpha]_D$ = +1.5 ($c$ = 1.0, MeOH). IR (ATR): $\tilde{\nu}$ = 3392 (br), 2917, 2849, 1742, 1693, 1648, 1461, 1259, 1017 $cm^{-1}$. $^1H$ NMR (600 MHz, [D$_4$]methanol): $\delta$ = 7.96 (dd, $J$ = 8.4, 1.2 Hz, 2 H, H-Bz), 7.72 (m, $J$ = 7.3, 1.2 Hz, 1 H, H-Bz), 7.69 (q, $^4J_{H,H}$ = 1.1 Hz, 1 H, 6-H), 7.56 (dd, $J$ = 8.4, 7.3 Hz, 2 H, H-Bz), 4.28 (dddd, $J$ = 10.0, 10.0, 6.6, 6.6 Hz, 1 H, 4′′′-H), 4.11 (m, 3 H, 1′-H, 2′′-H, 5′′′-H), 3.96 (m, 1 H, 1′-H), 3.94 (m, 1 H, 3′′-H), 3.63 (dd, $J$ = 8.1, 6.6 Hz, 1 H, 5′′′-H), 2.80 (dddd, $J$ = 10.0, 10.0, 6.1, 6.1 Hz, 1 H, 1′′-H), 2.39 (dddd, $J$ = 10.0, 10.0, 4.3, 0.8 Hz, 1 H, 4′′-H), 1.93 (d, $^4J_{H,H}$ = 1.1 Hz, 3 H, C$H_3$-C-5), 1.39 (s, 3 H, C$H_3$-C-2′′′), 1.33 (s, 3 H, C$H_3$-C-2′′′) ppm. $^{13}C$ NMR (90 MHz, [D$_4$]methanol): $\delta$ = 170.4 (C=O, Bz), 165.2 (C=O, C-4), 151.7 (C=O, C-2), 143.7 (CH, C-6), 136.2 (CH, Bz), 133.0 (C, Bz), 131.5 (CH, Bz), 130.4 (CH, Bz), 110.9 (C, C-5), 110.5 (C, C-2′′′), 75.9 (CH, C-4′′′), 71.1 (CH, C-2′′), 70.1 (CH, C-3′′), 69.4 (CH$_2$, C-5′′′), 48.8 (CH$_2$, C-1′), 47.1 (CH, C-4′′), 43.2 (CH, C-1′′), 27.3 (CH$_3$, $C$H$_3$-C-2′′′), 25.8 (CH$_3$, $C$H$_3$-C-2′′′), 12.3 (CH$_3$, $C$H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for $[C_{22}H_{26}N_2O_7 + Na]^+$453.1632; found 453.1641.

Data for **33**: $[\alpha]_D$ = –33.7 ($c$ = 0.9, MeOH). IR (ATR): $\tilde{\nu}$ = 3426 (br), 2923, 1745, 1692, 1642, 1442, 1258, 1056 $cm^{-1}$. $^1H$ NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.94 (d, $J$ = 8.1 Hz, 2 H, H-Bz), 7.75 (q, $^4J_{H,H}$ = 1.0 Hz, 1 H, 6-H), 7.71 (m, 1 H, H-Bz), 7.56 (dd, $J$ = 8.1, 8.1 Hz, 2 H, H-Bz), 4.69 (ddd, $J$ = 13.0, 6.7, 6.7 Hz, 1 H, 4′′′-H), 4.34 (ddd, $J$ = 5.5, 5.5, 2.5 Hz, 1 H, 2′′-H), 4.20 (m, 3 H, 1′-H, 3′′-H, 5′′′-H), 4.07 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 9.5 Hz, 1 H, 1′-H), 3.52 (dd, $^2J_{H,H}$ = 8.2, $^3J_{H,H}$ = 6.7 Hz, 1 H, 5′′′-H), 2.68 (m, 1 H, 1′′-H), 2.57 (m, 1 H, 4′′-H), 1.92 (d, $^4J_{H,H}$ = 1.0 Hz, 3 H, C$H_3$-C-5), 1.35 (s, 3 H, C$H_3$-C-2′′′), 1.33 (s, 3 H, C$H_3$-C-2′′′) ppm. $^{13}C$ NMR (100 MHz, [D$_4$]methanol): $\delta$ = 170.5 (C=O, Bz), 165.3 (C=O, C-4), 151.7 (C=O, C-2), 144.5 (CH, C-6), 136.2 (CH, Bz), 133.1 (C, Bz), 131.4 (CH, Bz), 130.4 (CH, Bz), 110.4 (C, C-5), 109.3 (C, C-2′′′), 75.7 (CH, C-4′′′), 71.3 (CH, C-2′′), 70.6 (CH$_2$, C-5′′′), 67.2 (CH, C-3′′), 48.0 (CH, C-4′′), 46.9 (CH$_2$, C-1′), 37.3 (CH, C-1′′), 27.3 (CH$_3$, $C$H$_3$-C-2′′′), 25.9 (CH$_3$, $C$H$_3$-C-2′′′), 12.3 (CH$_3$, $C$H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for $[C_{22}H_{26}N_2O_7 + Na]^+$ 453.1632; found 453.1641.

**1-({(1*R*,2*R*,3*S*,4*S*)-2,3-Dihydroxy-4-[(1*S*)-1,2-dihydroxyethyl]cyclobut-1-yl}methyl)thymine (9-T):** Diol **32** (22 mg, 0.05 mmol) was dissolved in MeOH (2.5 mL), and $p$-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol) was added. The resulting mixture was stirred for 4 h at room temp. Then, the reaction mixture was passed through a basic anion-exchange resin. The organic solution was concentrated under reduced pressure, and the residue was used for the following step without further purification.

The residue was dissolved in $MeNH_2$ (33% solution in EtOH; 0.5 mL), and the mixture was stirred at room temp. for 2 h. The volatiles were removed under reduced pressure, the residue was dissolved in Milli-Q water (2 mL), and the mixture was extracted with $CH_2Cl_2$ (3× 2.5 mL). The aqueous phase was concentrated under vacuum, and the resulting residue was then dissolved in MeOH. The MeOH solution was passed through an acidic cation-exchange resin. The organic solvent was evaporated under reduced pressure to obtain thymine nucleoside derivative **9-T** (6 mg, 0.02 mmol, 40%) as a white foam. $[\alpha]_D$ = –17.7 ($c$ = 0.9, MeOH). IR (ATR): $\tilde{\nu}$ = 3364 (br), 1677, 1475, 1260, 1091 $cm^{-1}$. $^1H$ NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.48 (q, $^4J_{H,H}$ = 1.2 Hz, 1 H, 6-H), 4.07 (m, 3 H, 1′-H, 2′′-H, 3′′-H), 3.95 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.1 Hz, 1 H, 1′-H), 3.75 (ddd, $^3J_{H,H}$ = 9.5, 6.9, 3.5 Hz, 1 H, 1′′′-H), 3.64 (dd, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 3.5 Hz, 1 H, 2′′′-H), 3.44 (dd, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 6.9 Hz, 1 H, 2′′′-H), 2.56 (m, 1 H, 1′′-H), 2.48 (m, 1 H, 4′′-H), 1.87 (d, $^4J_{H,H}$ = 1.2 Hz, 3 H, C$H_3$-C-5) ppm. $^{13}C$ NMR (100 MHz, [D$_4$]methanol): $\delta$ = 166.9 (C=O, C-4), 153.3 (C=O, C-2), 143.2 (CH, C-6), 111.1 (C, C-5), 72.6 (CH, C-1′′′), 71.1 (CH, C-2′′), 69.7 (CH, C-3′′), 66.4 (CH$_2$, C-2′′′), 48.1 (CH$_2$, C-1′), 47.1 (CH, C-4′′), 41.9 (CH, C-1′′), 12.2 (CH$_3$, $C$H$_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for $[C_{12}H_{18}N_2O_6 + Na]^+$ 309.1057; found 309.1061.

**1-({(1*R*,2*S*,3*R*,4*S*)-2,3-Dihydroxy-4-[(1*S*)-1,2-dihydroxyethyl]cyclobut-1-yl}methyl)thymine (10-T):** Diol **33** (25 mg, 0.06 mmol) was dissolved in MeOH (2.8 mL), $p$-toluenesulfonic acid monohydrate (12 mg, 0.06 mmol) was added, and the resulting mixture was stirred for 6 h at room temp. Then the reaction mixture was passed through a basic anion-exchange resin (Dowex 1X8 chloride form, 20–50 mesh). The organic solution was concentrated under reduced pressure, and the residue was used for the following step without further purification. The resulting crude was dissolved with a 33% solution of $MeNH_2$ in EtOH (0.5 mL) and the mixture was stirred at room temp. for 1 h. The volatiles were removed under reduced pressure, and the crude was dissolved with Milli-Q water (2 mL) and extracted with $CH_2Cl_2$ (3× 2.5 mL). The aqueous layer was concentrated under vacuum, and the resulting crude was then dissolved with MeOH and passed through an acidic cation-exchange resin (Dowex 50WX8 hydrogen form, 200–400 mesh). The organic solvent was evaporated under reduced pressure to give thymine nucleoside derivative **10-T** (9.5 mg, 0.03 mmol, 57%) as a white foam. $[\alpha]_D$ = –61.6 ($c$ = 1.0, MeOH). IR (ATR): $\tilde{\nu}$ = 3370 (br), 1672, 1476, 1219, 1126 $cm^{-1}$. $^1H$ NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.57 (q, $^4J_{H,H}$ = 1.1 Hz, 1 H, 6-H), 4.25 (m, 2 H, 1′-H, 3′′-H), 4.19 (m, 2 H, 1′-H, 2′′-H), 4.06 (ddd, $^3J_{H,H}$ = 9.8, 6.1, 3.7 Hz, 1 H, 1′′′-H), 3.68 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 3.7 Hz, 1 H, 2′′′-H), 3.45 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 6.1 Hz, 1 H, 2′′′-H), 2.80 (m, 1 H, 1′′-H), 2.40 (m, 1 H, 4′′-H), 1.86 (d, $^4J_{H,H}$ = 1.1 Hz, 3 H, C$H_3$-C-5) ppm. $^{13}C$ NMR (100 MHz, [D$_4$]methanol): $\delta$ = 166.9 (C=O, C-4), 153.3 (C=O, C-2), 144.3 (CH, C-6), 110.4 (C, C-5), 70.7 (CH, C-3′′), 69.9

(CH, C-1′′′), 68.5 (CH, C-2′′), 66.8 ($CH_2$, C-2′′′), 46.8 ($CH_2$, C-1′), 41.8 (CH, C-4′′), 41.1 (CH, C-1′′), 12.2 ($CH_3$, $CH_3$-C-5) ppm. HRMS (ESI$^+$): calcd. for $[C_{12}H_{18}N_2O_6 + Na]^+$ 309.1057; found 309.1061.

**9-({(1*R*,2*S*,3*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobutyl}methyl)-6-chloro-9*H*-purin-2-amine (34):** DBAD (94 mg, 0.41 mmol) was added to a solution of $PPh_3$ (113 mg, 0.41 mmol) in dry THF (3 mL), and the resulting solution was stirred at room temp. for 30 min. Then, a suspension of **14** (91 mg, 0.21 mmol) and 2-amino-6-chloropurine (70 mg, 0.41 mmol) in dry THF (3 mL) was added to the initial solution, and the resulting mixture was stirred overnight at room temp. Evaporation of the solvent and purification by column chromatography (hexane/diethyl ether, 2:1) gave **34** (106 mg, 0.18 mmol, 87%) as a brownish oil. $[\alpha]_D$ = +27.9 (*c* = 0.98, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3322, 2931, 1610, 1561, 1460, 1151, 1110, 1052 cm$^{-1}$. $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ = 7.86 (s, 1 H, 8-H), 7.62–7.52 (m, 4 H, Ph), 7.47–7.31 (m, 6 H, Ph), 5.13 (br. s, 2 H, $NH_2$), 4.74 (ddd, $^3J_{H,H}$ = 10.9, 6.4, 6.4 Hz, 1 H, 4′′′-H), 4.40 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.4 Hz, 1 H, 5′′′-H), 4.32 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.7 Hz, 1 H, 1′-H), 4.20 (ddd, $^3J_{H,H}$ = 7.5, 7.5, 7.5 Hz, 1 H, 3′′-H), 4.08 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 3.67 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.4 Hz, 1 H, 5′′′-H), 2.66 (ddd, $^3J_{H,H}$ = 10.9, 7.5, 7.5 Hz, 1 H, 2′′-H), 2.41–2.23 (m, 1 H, 1′′-H), 1.97–1.87 (m, 2 H, 2 4′′-H), 1.42 (s, 3 H, C$H_3$-C-2′′′), 1.38 (s, 3 H, C$H_3$-C-2′′′), 1.05 [s, 9 H, (C$H_3$)$_3$C] ppm. $^{13}$C NMR (62.5 MHz, $CDCl_3$): $\delta$ = 159.0 (C, C-2), 153.9 (C, C-4), 151.1 (C, C-6), 143.3 (CH, C-8), 135.8 (2 CH, Ph), 135.5 (2 CH, Ph), 133.5 (C, Ph), 133.1 (C, Ph), 130.1 (CH, Ph), 130.1 (CH, Ph), 128.0 (2 CH, Ph), 127.9 (2 CH, Ph), 125.4 (C, C-5), 108.4 (C, C-2′′′), 73.0 (CH, C-4′′′), 70.4 ($CH_2$, C-5′′′), 64.7 (CH, C-3′′), 49.6 (CH, C-2′′), 45.5 ($CH_2$, C-1′), 36.5 ($CH_2$, C-4′′), 29.1 (CH, C-1′′), 27.0 [3 $CH_3$, (C$H_3$)$_3$C], 27.0 ($CH_3$, C$H_3$-C-2′′′), 25.8 ($CH_3$, C$H_3$-C-2′′′), 19.0 [C, (CH$_3$)$_3$*C*] ppm. HRMS (ESI$^+$): calcd. for $[C_{31}H_{38}ClN_5O_3Si + Na]^+$ 614.2325; found 614.2330.

**(1*S*)-1-{(1*R*,2*R*,4*S*)-2-[(2-Amino-6-methoxy-9*H*-purin-9-yl)methyl]-4-hydroxycyclobutyl}-1,2-ethanediol (7-G$^{OMe}$):** Compound **34** (106 mg, 0.18 mmol) was dissolved in MeOH (6 mL), and *p*-toluenesulfonic acid (34 mg, 0.18 mmol) was added. The solution was heated at reflux overnight. Then the solution was cooled to room temp., passed through DOWEX 1X8 resin, concentrated under reduced pressure, and purified by column chromatography (EtOAc to EtOAc/MeOH, 9:1) to give **7-G$^{OMe}$** (45 mg, 0.15 mmol, 82%) as a white solid, m.p. 155–157 °C (MeOH). $[\alpha]_D$ = –12.0 (*c* = 0.81, MeOH). IR (ATR): $\tilde{\nu}$ = 3500–3000, 2922, 2852, 2361, 1641, 1606, 1587, 1483, 1398, 1248, 1066 cm$^{-1}$. $^1$H NMR (400 MHz, [D$_4$]methanol): $\delta$ = 7.85 (s, 1 H, 8-H), 4.53 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 5.2 Hz, 1 H, 1′-H), 4.38 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 9.8 Hz, 1 H, 1′-H), 4.24 (ddd, $^3J_{H,H}$ = 6.7, 6.7, 1.3 Hz, 1 H, 4′′-H), 4.19 (ddd, $^3J_{H,H}$ = 10.0, 6.3, 3.8 Hz, 1 H, 1′′′-H), 4.04 (s, 3 H, C$H_3$O-C-6), 3.80 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 3.8 Hz, 1 H, 2′′′-H), 3.49 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 6.3 Hz, 1 H, 2′′′-H), 2.73–2.59 (m, 2 H, 1′′-H, 2′′-H), 2.28–2.20 (m, 1 H, 3′′-H), 1.86 (ddd, $^2J_{H,H}$ = 11.7, $^3J_{H,H}$ = 7.3, 6.7 Hz, 1 H, 3′′-H) ppm. $^{13}$C NMR (100 MHz, [D$_4$]methanol): $\delta$ = 162.7 (C, C-6), 161.7 (C, C-2), 155.0 (C, C-4), 141.3 (CH, C-8), 115.2 (C, C-5), 70.0 (CH, C-1′′′), 67.2 ($CH_2$, C-2′′′), 66.1 (CH, C-4′′), 54.1 ($CH_3$, C$H_3$O-C-6), 47.1 ($CH_2$, C-1′), 46.7 (CH, C-1′′), 35.4 ($CH_2$, C-3′′), 32.2 (CH, C-2′′) ppm. HRMS (ESI$^+$): calcd. for $[C_{13}H_{19}N_5O_4 + Na]^+$ 332.1329; found 332.1329.

***N*,*N*-Bis(*tert*-butoxycarbonyl)-2-amino-6-chloro-9-({(1*R*,4*S*)-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclobut-2-en-1-yl}methyl)purine (35):** A solution of DBAD (148 mg, 0.64 mmol) in dry THF (1.8 mL) was added dropwise to a stirred suspension of alcohol **17** (59 mg, 0.32 mmol), *N*,*N*-bis(*tert*-butoxycarbonyl)-2-amino-6-chloropurine (239 mg, 0.64 mmol), and $PPh_3$ (168 mg, 0.64 mmol) in anhydrous THF (2.3 mL) under an argon atmosphere at 0 °C. The mixture was allowed to warm to room temp. and stirred overnight. The organic solvent was removed under vacuum, and the resulting oil was purified by column chromatography (hexane/EtOAc, 10:1 to 1:1) to give **35** (103 mg, 0.19 mmol, 60%) as a pale yellow solid, m.p. 44–47 °C ($CHCl_3$). $[\alpha]_D$ = +11.1 (*c* = 1.1, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2961, 2921, 1723, 1369, 1260, 1094, 1020 cm$^{-1}$. $^1$H NMR (360 MHz, $CDCl_3$): $\delta$ = 8.27 (s, 1 H, 8-H), 6.16 (d, $^3J_{H,H}$ = 2.9 Hz, 1 H, 2′′-H), 6.00 (d, $^3J_{H,H}$ = 2.9 Hz, 1 H, 3′′-H), 4.59 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 6.5 Hz, 1 H, 1′-H), 4.43 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 8.4 Hz, 1 H, 1′-H), 4.15 (m, 2 H, 5′′′-H, 4′′′-H), 3.69 (ddd, $^2J_{H,H}$ = 9.2, $^3J_{H,H}$ = 9.2, 6.5 Hz, 1 H, 5′′′-H), 3.49 (ddd, $^3J_{H,H}$ = 8.4, 6.5, 4.2 Hz, 1 H, 1′′-H), 3.10 (dd, $^3J_{H,H}$ = 9.2, 4.2 Hz, 1 H, 4′′-H), 1.44 [s, 18 H, 2 (C$H_3$)$_3$CO], 1.40 (s, 3 H, C$H_3$-C-2′′′), 1.35 (s, 3 H, C$H_3$-C-2′′′) ppm. $^{13}$C NMR (90 MHz, $CDCl_3$): $\delta$ = 153.0 (C, C-4), 151.8 (C, C-2/C-6/C=O Boc), 151.1 (C, C-2/C-6/C=O Boc), 150.8 (C, C-2/C-6/C=O Boc), 146.7 (CH, C-8), 139.5 (CH, C-2′′), 137.0 (CH, C-3′′), 130.2 (C, C-5), 109.9 (C, C-2′′′), 83.7 [2 C, (CH$_3$)$_3$*C*O], 76.00 (CH, C-4′′′), 68.7 ($CH_2$, C-5′′′), 49.7 (CH, C-4′′), 45.6 (CH, C-1′′), 44.8 ($CH_2$, C-1′), 28.0 [6 $CH_3$, (C$H_3$)$_3$CO], 27.0 ($CH_3$, C$H_3$-C-2′′′), 25.8 ($CH_3$, C$H_3$-C-2′′′) ppm. HRMS (ESI$^+$): calcd. for $[C_{25}H_{34}ClN_5O_6 + Na]^+$ 558.2090; found 558.2087.

***N*,*N*-Bis(*tert*-butoxycarbonyl)-2-amino-6-chloro-9-({(1*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]cyclobut-2-en-1-yl}methyl)purine (36):** Compound **35** (28 mg, 0.05 mmol) was dissolved in MeOH (2.3 mL), *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol) was added, and the resulting mixture was stirred for 24 h at room temp. After removal of the solvent, the residue was purified by column chromatography (hexane/EtOAc, 1:1, to EtOAc/MeOH, 9:1) to give **36** (18 mg, 0.04 mmol, 69%) as a white solid, m.p. 58–62 °C ($CHCl_3$). $[\alpha]_D$ = –3.2 (*c* = 0.9, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2960, 2927, 1736, 1562, 1368, 1260, 1099 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 8.25 (s, 1 H, 8-H), 6.15 (d, $^3J_{H,H}$ = 2.9 Hz, 1 H, 2′′-H), 6.07 (dd, $^3J_{H,H}$ = 2.9, 0.8 Hz, 1 H, 3′′-H), 4.67 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 7.2 Hz, 1 H, 1′-H), 4.45 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 6.6 Hz, 1 H, 1′-H), 3.74 (m, 1 H, 2′′′-H), 3.70 (m, 1 H, 1′′′-H), 3.54 (ddd, $^3J_{H,H}$ = 7.2, 6.6, 4.2 Hz, 1 H, 1′′-H), 3.49 (m, 1 H, 2′′′-H), 3.06 (ddd, $^3J_{H,H}$ = 10.3, 4.2, 0.8 Hz, 1 H, 4′′-H), 2.85 (br. s, 1 H, OH), 2.19 (br. s, 1 H, OH), 1.47 [s, 18 H, 2 (C$H_3$)$_3$CO] ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 153.2 (C, C-4), 151.7 (C, C-2/C-6/C=O Boc), 151.3 (C, C-2/C-6/C=O Boc), 151.1 (C, C-2/C-6/C=O Boc), 146.6 (CH, C-8), 138.2 (CH, C-2′′), 138.0 (CH, C-3′′), 130.0 (C, C-5), 84.2 [2 C, (CH$_3$)$_3$*C*O], 71.6 (CH, C-1′′′), 65.8 ($CH_2$, C-2′′′), 48.6 (CH, C-4′′), 46.2 (CH, C-1′′), 44.4 ($CH_2$, C-1′), 28.1 [6 $CH_3$, (C$H_3$)$_3$CO] ppm. HRMS (ESI$^+$): calcd. for $[C_{22}H_{30}N_5O_6Cl + Na]^+$ 518.1777; found 518.1782.

**9-({(1*R*,4*S*)-4-[(1*S*)-1,2-Dihydroxyethyl]cyclobut-2-en-1-yl}methyl)-guanine (8-G):** Compound **35** (32 mg, 0.06 mmol) was dissolved in MeOH (1.4 mL), and HCl (1 N aq.; 1.20 mL) was added. The mixture was stirred at room temp. for 70 h, then it was neutralized with NaOH (1 N). The resulting mixture was added dropwise to diethyl ether (18 mL). The mixture was cooled to 5 °C, and a precipitate formed. The resulting solid was separated from the organic solvent by decantation, then it was dried under vacuum to give **8-G** (15 mg, 0.05 mmol, 90%) as a pale yellow solid, m.p. > 280 °C (MeOH). $[\alpha]_D$ = –126.4 (*c* = 1.1, MeOH). IR (ATR): $\tilde{\nu}$ = 3315 (br), 3175 (br), 2922, 1700, 1634, 1590, 1368, 1058 cm$^{-1}$. $^1$H NMR (250 MHz, [D$_4$]methanol): $\delta$ = 9.08 (s, 1 H, 8-H), 6.18 (m, 2 H, 2′′-H, 3′′-H), 4.61 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 7.4 Hz, 1 H, 1′-H), 4.37 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 8.1 Hz, 1 H, 1′-H), 3.65 (m, 3 H, 1′′′-H, 2′′′-H,

1′′-H), 3.51 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 6.8 Hz, 1 H, 2′′′-H), 3.08 (dd, $J$ = 10.0, 4.2 Hz, 1 H, 4′′-H) ppm. $^{13}$C NMR (62.5 MHz, [D$_4$]-methanol): $\delta$ = 157.2 (C, C-2/C-6), 155.1 (C, C-2/C-6), 151.8 (C, C-4), 139.5 (CH, C-2′′/C-3′′), 138.8 (CH, C-2′′/C-3′′), 138.5 (CH, C-8), 108.6 (C, C-5), 73.2 (CH, C-1′′′), 66.5 ($CH_2$, C-2′′′), 49.8 (CH, C-4′′), 47.1 ($CH_2$, C-1′), 45.8 (CH, C-1′′) ppm. HRMS (ESI$^+$): calcd. for $[C_{12}H_{15}N_5O_3 + Na]^+$ 300.1067; found 300.1072.

**Supporting Information** (see footnote on the first page of this article): Experimental details for the synthesis of intermediate **14**, crystallographic data, antiviral activity assays, details of computational methods, and $^1$H and $^{13}$C NMR spectra of all new compounds. CCDC-936649 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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