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Synthesis, antiviral evaluation and computational studies of cyclobutane and cyclobutene L-nucleoside analogues

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The present work describes the stereoselective synthesis of a series of different functionalized cyclobutane and cyclobutene L-nucleoside analogues (L-NAs) featuring a methylene spacer between the carbocycle and the nucleobase. These L-nucleosides were subjected to comprehensive screening for antiviral activity. In order to obtain molecular knowledge relevant for further synthetic designs, the mechanism of action of these L-nucleoside analogues as anti-HSV agents was investigated by computational approaches. In particular, protein-ligand docking calculations were used to rationalize the ability of the prodrug candidates to get activated. Dockings were performed on the three kinases involved in the activation process of the thymine and guanine derivatives.

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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 interest in the development of novel nucleoside analogues with high potency, low toxicity, and favorable resistance profiles. The search for more active nucleoside analogues has been primarily focused 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 have enhanced lipophilicity compared to regular nucleosides, favoring absorption and penetration through the cell membrane. Additionally, carbocyclic nucleosides often display modified conformational properties in comparison to standard furanose nucleosides. The cyclopentenyl nucleosides Carbovir,[3] **1,** Abacavir,[4] **2**, and the cyclobutyl nucleoside Lobucavir,[5] **3**, are among the earlier successful examples (Figure 1). In particular, since the discovery of the high antiviral activity of Lobucavir, the synthesis and antiviral activity of cyclobutane nucleoside analogues have been the subject of close scrutiny by several groups including ours.[6]

Other modifications have led to the discovery of the antiviral activity of L-nucleoside analogues (L-NAs).[7] Several of these analogues such as Lamivudine,[8] **4**, Emtricitabine,[9] **5**, and Telbivudine,[10] **6**, have shown potent activities against a wide range of viral infections with mild toxicity. The antiviral activity of some unnatural L-nucleosides evidenced that not all the enzymes involved in phosphorylation processes are completely enantioselective. Actually, this relaxed enantioselectivity has been perceived as a potential antiviral strategy, favoring the use of L-nucleosides since they may provide a better toxicological profile along with greater stability against cellular enzymes compared to 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 former experience and 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. Herein we describe the synthesis and antiviral activity of the cyclobutane and cyclobutene L-NAs **7-11**. These analogues, besides 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, in order to rationalize the activity experimentally observed, we have merged our synthetic developments with molecular modeling. These studies include

ligand- and structure-based approaches on the synthesized analogues with the active site of viral and cellular kinases.

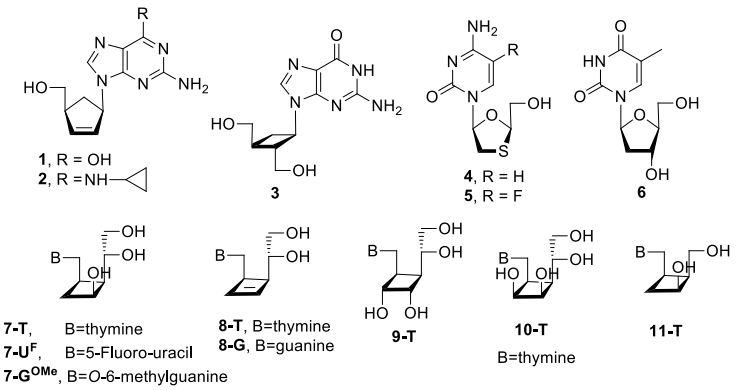
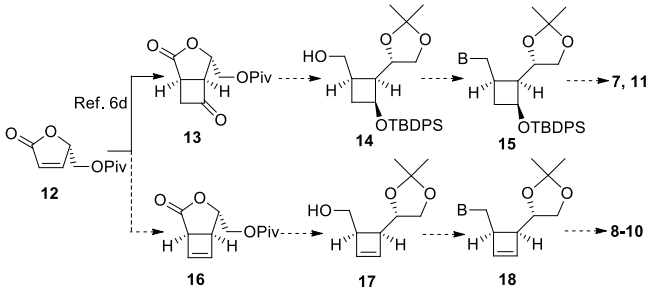


Figure 1. Selected carbocyclic and L-nucleoside analogues **1-6** and synthesized cyclobutane L-nucleoside analogues **7-11**.

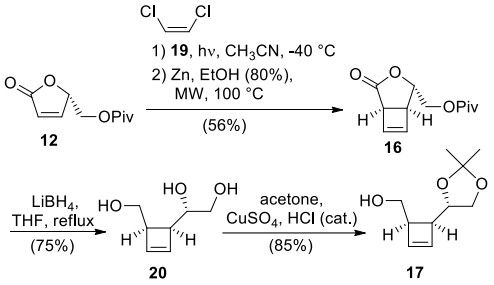
Results and Discussion

Our synthetic plan (Scheme 1) involved the diastereoselective construction of the cyclobutane or cyclobutene ring through a [2 + 2] photochemical reaction of the enantiopure 2(5*H*)-furanone **12** followed by the conversion of the cycloadducts **13** and **16** to the key intermediates **14** and **17**. Both alcohols **14** and **17** were envisaged to be suitable substrates to introduce the selected nucleobases via a Mitsunobu reaction to produce **15** and **18** and eventually the carbocyclic L-nucleoside analogues **7-11**.



Scheme 1. Synthetic strategy to cyclobutane and cyclobutene L-NAs

Accordingly, our initial efforts focused on the preparation of the pivotal intermediates **14** and **17**. The synthesis of the new cyclobutene intermediate **17** (Scheme 2) started with the [2 + 2] photocycloaddition of the 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 furnish the bicycle **16**, derived from the major anti cycloadducts in 56% overall yield. Formation of the triol **20** by exhaustive reduction of **16** was accomplished in 75% yield using $LiBH_4$ in THF at the 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 $CuSO_4$ affording the cyclobutene intermediate **17** in excellent yield. The known alcohol **14** was prepared in a similar way in 28% yield from **12**, following our previously described synthetic sequence which has been refined and improved (see Supporting Information).[6d]

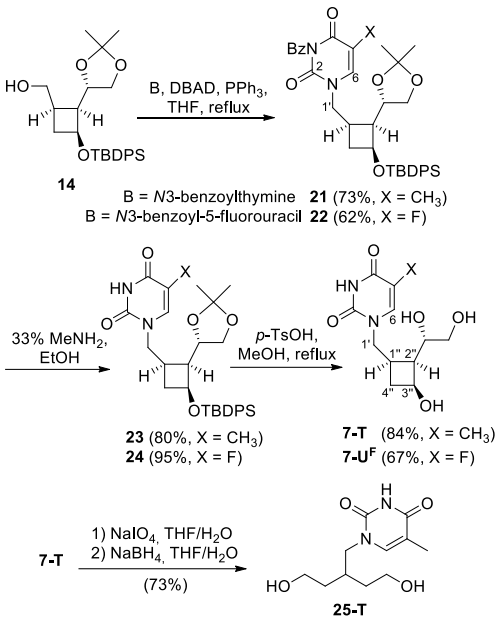


Scheme 2. Synthesis of intermediate **17**.

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 in THF at the reflux temperature delivered **21** in 73% yield. The fluorine-containing nucleoside **22** was prepared in 62% yield in the same manner by treatment of the alcohol **14** with *N*3-benzoyl-5-fluorouracil.[17,18] It is worth to notice that reaction of the bases with the corresponding mesylate via a classic S_N2 reaction gave lower yields of **21** and **22**. The *N*1 site attachment of the base in **21** and **22** could be confirmed by their HMBC spectra, which showed correlation between H-1' and both C-2 and C-6 and also between C-1' and H-6. The syntheses of the L-nucleosides **7-T** and **7-U^F** from **21** and **22** required deprotection of *N*3 and the three hydroxyl groups. First, cleavage of the *N*3-protecting group was achieved by reaction of **21** with a 33% $MeNH_2$ solution in EtOH.[17] The reaction proceeded smoothly at rt, giving **23** in 80% yield. Then, simultaneous removal of the acetonide and the silyl protections by treatment of **23** with *p*-TsOH in MeOH at the reflux temperature furnished the target nucleoside **7-T** in 84% yield. The synthesis of the fluorouracil nucleoside **7-U^F** was carried out in an analogous manner in 64% yield for the two steps. The NOESY spectra of **7-T** and **7-U^F** evidence the relative configuration of the stereogenic centres of the cyclobutane ring, since proton H-1'' displays cross peaks with H-3'' and H-4''.

We then undertook the synthesis of the hydroxymethyl derivative **11-T** which a priori would involve the oxidative cleavage of the diol present in **7-T**, followed by reduction of the

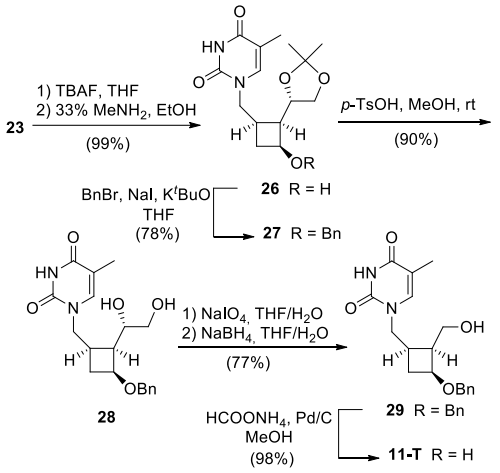
corresponding aldehyde. However, when diol **7-T** was submitted to standard oxidative cleavage/reduction conditions, only the acyclic compound **25-T** was isolated in 73% yield. The formation of **25-T** can be rationalized in terms of a retro-aldol reaction of the originally formed β–hydroxy aldehyde, followed by the reduction of both aldehyde groups. In order to avoid the formation of this acyclic product, other oxidative cleavage methodologies were explored. Our attempts, including treatment with $Pb(OAc)_4$ or $Mn(OAc)_3$[19] or a combination of KIO_4 and $KHCO_3$ in a buffered solution at pH 7-7.5,[20] either led to **25-T** or afforded complex mixtures of products.



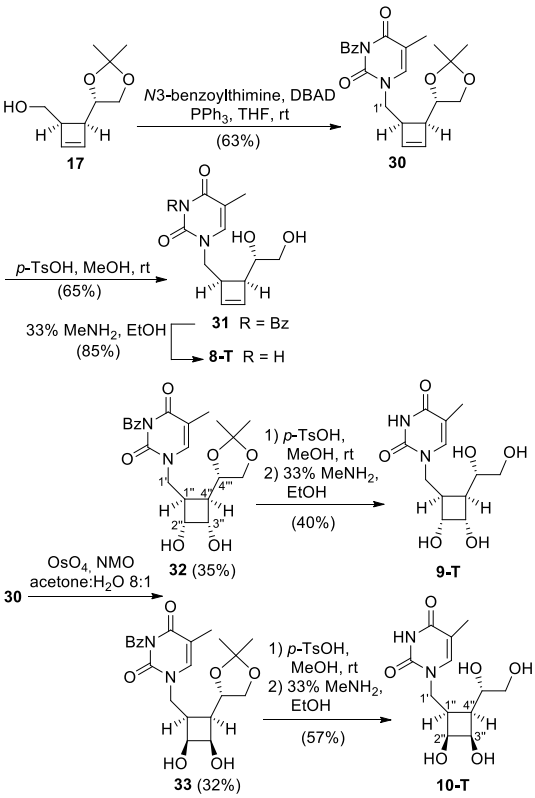
Scheme 3. Preparation of the cyclobutane L-NAs **7-T** and **7-U^F** and attempts to oxidative cleavage of **7-T**.

In view of these results, we pursued an alternative route to prepare **11-T** keeping the cyclobutane alcohol protected during the oxidative cleavage step to guarantee the integrity of the cyclobutane moiety (Scheme 4). In the event, desilylation of **23** with TBAF followed by nucleobase deprotection furnished alcohol **26** in almost quantitative yield. Benzylation of the hydroxyl group of **26** was accomplished by treatment with BnBr, NaI and K^{t}BuO in THF. Next, **27** was exposed to a mild acid medium to induce acetonide hydrolysis to deliver in 90% yield diol **28**, which was submitted to an oxidative cleavage and subsequent reduction rendering the corresponding hydroxymethyl derivative **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 the target nucleoside **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 an X-ray crystallographic analysis.

We then directed our attention to the preparation of the 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 the target cyclobutene nucleoside analogue **8-T** in 35% global yield. At this point, it was decided to further functionalize the cyclobutane double bond. To this end, the fully protected compound **30** was subjected to dihydroxylation under mild conditions[22] by reaction with NMO and catalytic OsO_4 in acetone-H_2O producing a chromatographically separable mixture of diols **32** and **33** in 35% and 32% yield, respectively. The relative configuration of diol **32** was assigned on the basis of NOE experiments that showed enhancement of the cyclobutane proton H-3'' proton upon irradiation of H-4'''. Unfortunately, the chemical shifts of the key protons of **33** are almost identical and unequivocal NOE signals between these protons could not be determined, but its relative configuration was proven in the final product **10-T**. Thus, sequential removal of the acetonide and the benzoyl protecting groups in **32** and **33** furnished the cyclobutane tetrols L-NAs **9-T** and **10-T** in 40% and 57% yield, respectively. The NOE analysis of **10-T** disclose its relative configuration. Hence, irradiation of proton H-4'' led to selective enhancements of H-2'' and H-3'' indicating that these protons are on the same side of the ring.

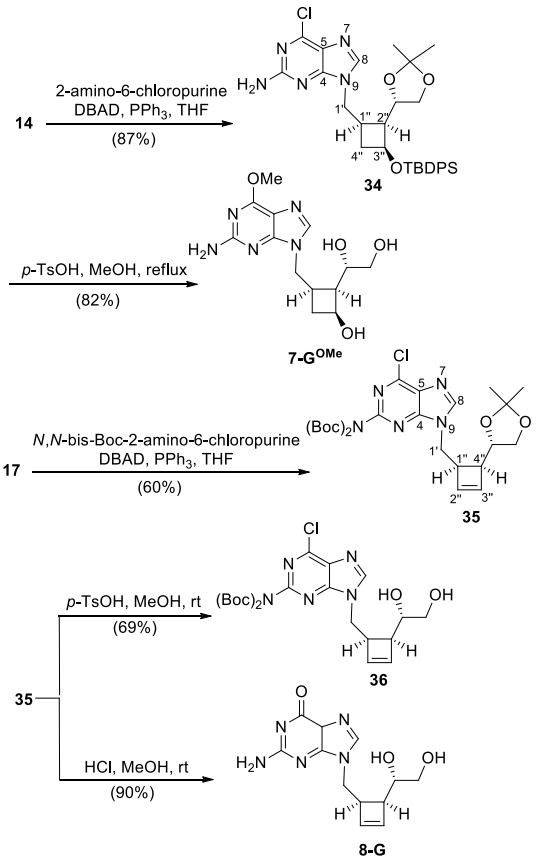


Scheme 4. Preparation of the cyclobutane L-NA **11-T**.



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

Next, we focused on the synthesis of the purine cyclobutane and cyclobutene L-nucleoside analogues starting from **14** and **17** and following a similar strategy as above (Scheme 6). The Mitsunobu reaction of alcohol **14** with 2-amino-6-chloropurine, that was chosen because of its easy conversion into either guanine[23] or its 6-*O*-methyl derivative,[24,25] afforded exclusively the *N*9 regioisomer **34** in excellent yield (87%). The attachment site of the purine base was established by HMBC experiments, which showed correlation between carbon C-4 and proton H-1'. Then, we targeted the *O*6-methylguanine derivative to provide 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 the reflux temperature. Under these conditions, in addition to the expected alcohol deprotection, the chlorine was replaced by a methoxy group and the target nucleoside **7-G^{OMe}** was obtained in good yield.[27]



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

The synthesis of the 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 (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 to the corresponding guanine derivative **8-G** by simultaneous removal of the bis-Boc and acetonide protections and chlorine-oxigen exchanged by treatment with aqueous trifluoroacetic acid.[29] However, exposure of **35** to a mixture of 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 rt for 30 min generated exclusively the diol **36**, with no effect on the 6-chloro or the Boc protecting groups. Eventually, it was found that **35** could be converted to **8-G** in excellent yield upon treatment with HCl in MeOH at rt.[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) [herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, and herpes simplex virus-1 (TK-KOS ACVr)] cell cultures, in HeLa [vesicular stomatitis virus, coxsackie virus B4 and respiratory syncytial virus] cell cultures, in Vero [parainfluenza-3 virus, Reovirus-1, Sindbis virus, Coxsackie virus B4 and Punta Toro virus] cell cultures, in Crandell- Rees feline kidney (CRFK) [anti-feline corona virus and anti-Feline herpes virus] cell cultures and in Madin Darby canine kidney (MDCK) [anti-influenza A virus (H1N1, H3N2, H2N2); influenza B virus] cell cultures. None of the compounds exhibited significant antiviral activity or cytotoxicity.[31]

In order to gain antiviral activity, the prepared L-NAs require serial phosphorylation, via the mono- and the diphosphate intermediates, to the ultimately bioactive triphosphorylated form L-NA-TP.[32] This implies that, given the cyclobutane moiety and the inverted configuration, the activity of the cyclobutane L-NAs would be dependent on the capacity of all the enzymes of the activation pathway to phosphorylate analogues with carbocyclic scaffolds with opposite chirality, along with the ability of the L-NA-TP to successfully interact with the DNA polymerase. Therefore, the conversion of the L-NAs into their active L-NAs-TP is as important as the affinity of these analogues for the target DNA polymerase. Often the first phosphorylation transfer is the rate-limiting step because of the specificity of the involved nucleoside kinase, and an strategy to bypass this limitation could be the preparation of pronucleotides.[33] However, prior to perform further chemical synthesis it was decided to discern whether the phosphorylation of our analogs may be a prerequisite for antiviral activity. To that end, we undertook a molecular modeling study of compounds **7-10** and **25** on the whole activation process, focusing on HSV-1. To the best of our knowledge, this is the first study that investigates the three successive phosphoryl transfers on NAs in HSV-1 infected cells.

Molecular docking simulations were performed using the program GOLD (version 5.0)[34] on all 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 on crystallographic structures available with natural ligands, such as thymidine and guanosine, or with the known drug acyclovir. It is important to notice that carbocyclic nucleoside analogues **7-10** contain an additional hydroxymethyl moiety compared to regular nucleosides. As a result, two different activation pathways were envisaged, considering the three successive phosphoryl transfers 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 reactant form. Additionally, calculations with thymidine (dT) and acyclovir (ACV) were also performed to provide with a structural and energetic benchmark for pyrimidine and purine compounds, respectively. Docking results

were analyzed 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 or even lower than those of the reference compounds.

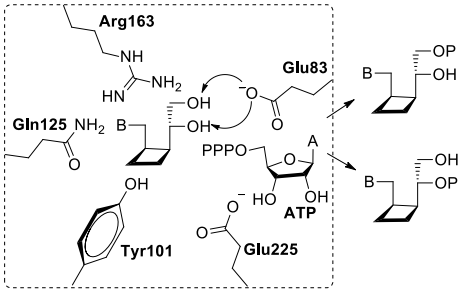
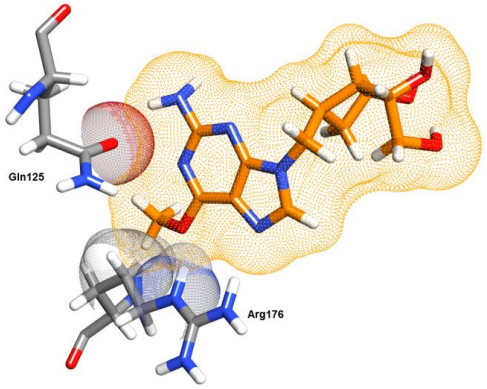


Figure 2. Representation of the two possible phosphorylation pathways of the studied compounds. An example is given for the first kinase involved in the activation process (HSV-1 thymidine kinase): upon abstraction of the corresponding proton by Glu83, nucleosides may be phosphorylated either at their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

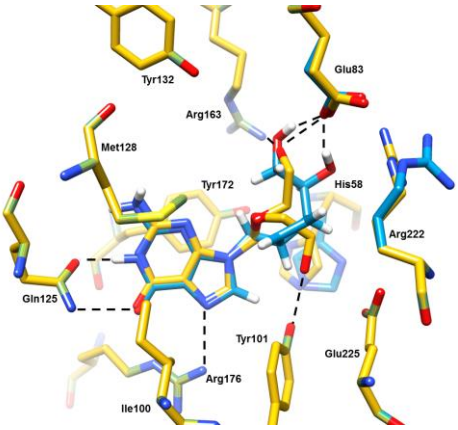
The first phosphorylation step was studied on the HSV-1 TK structure crystallized with dT in its binding site (PDB entry code: 1KIM[37]) for thymine derivatives and HSV-1 TK crystallized with ACV (PDB entry code: 2KI5[38]) for guanine derivatives. Docking calculations of the synthesized nucleosides led to three different behaviors (Tables 7 and 8, Supporting Information). 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 nucleosides present low energy solutions for which both 1'''-OH and 2'''-OH interact with the catalytic residue Glu83, responsible of deprotonating the alcohol to be phosphorylated, suggesting that both phosphorylation pathways could take place (Figure 3a).[35] Conversely, the lowest energy binding modes of compound **7-U^{F}** are compatible 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 assure the success in the phosphorylation of this compound. 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 proper orientation for the catalytic reaction (Figure 3b). This compound flips around to minimize these clashes, leaving either the base or the hydroxyl moieties outside their pockets. Therefore, the presence of a modified purine base in the studied compounds seems to be restrictive for the first activation step.



b)

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

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 in the study of guanine derivatives. The high sequence similarity between mouse and human GMPK guarantees that the information on the mouse enzyme is directly transferable to the human enzyme.[39] Accordingly, the structures selected to perform the calculations of this second activation step corresponded to HSV-1 TK crystallized with thymidine-5'-monophosphate (dTMP) and ADP (PDB entry code: 1VTK[40]) as well as 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 9 and 10, Supporting Information). Compounds **7-T**, **8-T** and **8-G** may be phosphorylated either at their 1''' or 2''' position, all of them maintaining the main interactions of the corresponding X-ray structures (Figure 4). By 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 in the activation by HSV-1 TK, since few binding modes are similar to the crystallographic ones and their binding energy values are higher than that of reference.



a)

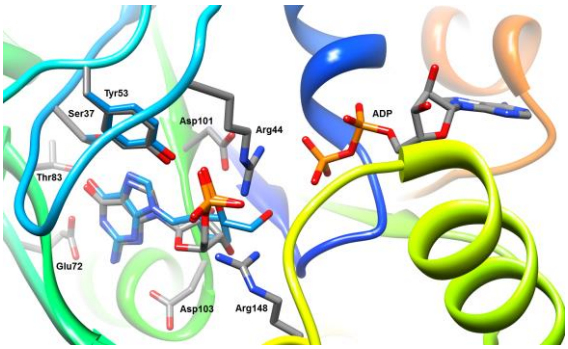


Figure 4. Overlap between the best binding mode of monophosphorylated **8-G** (blue) and crystallographic GMP (gray) in mouse GMPK binding site (PDB entry code: 1LVG). Crystallographic ADP is also shown. Hydrogen atoms and hydrogen bonds are not shown for clarity.

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: a complex of slime mold *Dictyostelium discoideum* NDPK with thymidine-5'-diphosphate (dTDP) (PDB entry code: 1NDC[41]), which has shown in many aspects similar behavior to its human counterpart, and human NDPK crystallized with guanosine-5'-diphosphate (GDP) (PDB entry code: 1NUE[42]) for pyrimidine and purine derivatives, respectively. It is worth to point out that since the binding sites of both NDPK are widely solvent exposed, docking calculations of the X-ray ligands into the corresponding structures do not reproduce the crystallographic structures as precisely as those of previous activation steps. Thus, the prediction based on this activation step should be read with caution. According to docking, the diphosphorylated derivatives of **7-T**, **8-T**, **10-T** and **8-G** show some binding modes consistent with the catalysis. Therefore all these analogues are likely to be phosphorylated to their active form by NDPK (Figure 5, Tables 11 and 12, Supporting Information).

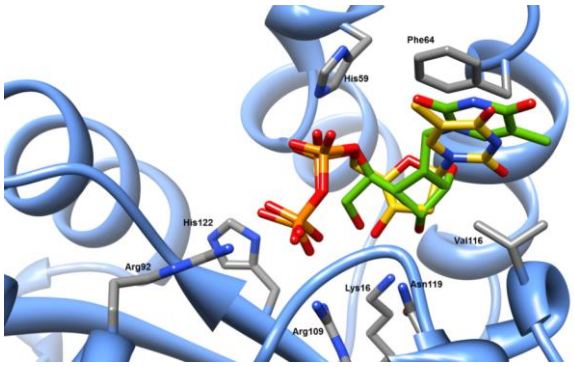


Figure 5. Overlap between the best binding mode of diphosphorylated **8-T** (green) and crystallographic dTDP (yellow) in *Dictyostelium discoideum* NDPK binding site (PDB entry code: 1NDC). Hydrogen atoms are not shown for clarity.

Conclusions

To sum up, a synthetic strategy for the stereoselective preparation of several enantiopure functionalyzed cyclobutane L-nucleosides 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 exhibited significant antiviral activity or cytotoxicity. Molecular modeling studies were performed on the whole activation process of the synthesized analogues to find out if this process could be a determining factor for their poor activity against HSV-1. The theoretical results show that nucleosides **7-U^{F}**, **7-G^{OMe}**, **9-T** and **25-T** clearly fail in their activation process, 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 form, the lack of activity against HSV-1 might be due either to the chemical deactivation of their triphosphorylated forms or to the failure in their incorporation into the viral DNA strand, carried out by HSV-1 DNA polymerase. Unfortunately, this last process has not been possible to study due to the lack of HSV-1 DNA polymerase structures crystallized with DNA. Work is in progress to use homology modeling to generate this complex.

Experimental Section

General: Commercially available 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 GC when needed. Flash column chromatography was performed using silica gel (230-400 mesh) unless otherwise indicated within the text. Filtrations through basic anion exchange resins were carried out on Dowex® 1X8 resin (chloride form, 20-50 mesh). Filtrations through acidic cation exchange resins were performed on Dowex® 50WX8 resin (hydrogen form, 200-400 mesh). ^{1}H NMR 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 (δ) ($CDCl_3$, δ 7.26 or CD_3OD, δ 3.31). Carbon chemical shifts are reported in ppm (δ) ($CDCl_3$, δ 77.2 or CD_3OD, δ 49.0). NMR signals were assigned with the help of COSY, HSQC, HMBC, DEPT135, selective NOE and NOESY experiments. Infrared peaks are reported in cm^{-1}. Melting points were determined on hot stage and are uncorrected. HRMS were recorded with a mass spectrometer. Optical rotations were measured at 22 ± 2 °C.

Microwave reactions were conducted on a CEM Discover™ Microwave synthesizer. The machine consists of a continuous focused microwave-power delivery system with 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. All experiments were performed using a stirring option whereby the contents of the vessel were stirred by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir 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, H3N2), influenza virus B, Reovirus-1, Sindbis and Punta Toro. 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) or Madin-Darby canine kidney cells (MDCK). Confluent cell cultures in microtiter 96-well plates were inoculated with 100 CCID50 of virus (1 CCID50 being the virus dose 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 were not treated with the test compounds. Antiviral activity was expressed as the EC50 or compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%.

Molecular modeling. The binding modes and energies were predicted using protein-ligand dockings algorithms. Those 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 the MMFF minimization. For each PDB structure, all crystallographic waters, 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 center of binding site in the crystallographic structure was used as the central point for the cavity. 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 studied compounds. Each compound was docked into the corresponding enzyme and 20 predicted poses 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 passage of 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 throughout the refrigeration jacket. The mixture was irradiated using a medium pressure 400W mercury lamp (400W MP mercury lamp 3040, photochemical reactors LTD) for 7 h. The progress of the reaction was monitored by GC. Then, the crude was concentrated under reduced pressure, dissolved with hexane-EtOAc 1:1 and passed through a silica gel pad. Evaporation of the solvent under reduced pressure provided a diastereomeric mixture of the dichlorocyclobutane derivatives that was used for the following step without further purification. Thus, the mixture was spited in three portions and each one was dissolved in 80% aqueous EtOH (4 mL) and activated Zn dust (3.6 g, 55 mmol) was added. Each mixture was irradiated under pressure in a focused microwave reactor at 100 °C for 15 min. After cooling, the combined reaction mixture was filtered through Celite. The solid was washed several times with EtOH and EtOAc. Evaporation of the solvent gave a residue, which was subjected to column chromatography (hexane-EtOAc 6:1) to provide **16** (1.16 g, 5.17 mmol, 56% yield) as a colorless oil: $[\alpha]_D$ = -211.9 (*c* = 1.1, $CHCl_3$); IR (film): υ = 2975, 2874, 1768, 1734, 1484, 1284 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 6.35 (ddd, $^3J_{H,H}$ = 2.7, 0.7, $^4J_{H,H}$ = 0.5 Hz, 1H, 6-H), 6.30 (dd, $^3J_{H,H}$ = 2.7, 0.8 Hz, 1H, 7-H), 4.60 (dddd, $^3J_{H,H}$ = 3.0, 2.8, 1.5, $^4J_{H,H}$ = 0.5 Hz, 1H, 4-H), 4.26 (dd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 2.8 Hz, 1H, 8-H), 4.12 (dd, $^2J_{H,H}$ = 12.0, $^3J_{H,H}$ = 3.0 Hz, 1H, 8-H), 3.70 (dd, $^3J_{H,H}$ = 3.5, 0.8 Hz, 1H, 1-H), 3.45 (ddd, $^3J_{H,H}$ = 3.5, 1.5, 0.7 Hz, 1H, 5-H), 1.20 (s, 9H, (C*H*$_3$)$_3$C); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 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)$_3$*C*), 27.1 (CH_3, (*C*H$_3$)$_3$C). Anal. Calcd for $C_{12}H_{16}O_4$ requires 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): To a solution of **16** (462 mg, 2.06 mmol) in dry THF (34 mL), a 2.0 M solution of $LiBH_4$ in THF (5 mL, 10.00 mmol) was added dropwise under argon atmosphere. The mixture was heated up to 90 °C and stirred at this temperature for 4 h. Then, the reaction was allowed to cool to rt and quenched with $Na_2SO_4{\cdot}10H_2O$ until no bubbling was observed. The suspension was stirred overnight and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure and the crude was purified by column chromatography (from hexane-EtOAc 1:1 to CH_2Cl_2-MeOH 9:1) to afford **20** (252 mg, 1.74 mmol, 75% yield) as a colorless oil: $[\alpha]_D$ = +22.7 (*c* = 1.5, $CHCl_3$); IR (ATR): υ = 3293 (br), 2885, 1648, 1427, 1288, 1152, 1087 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$); δ = 6.04 (dd, $^3J_{H,H}$ = 2.9, 0.8 Hz, 1H, 2'-H), 6.02 (dd, $^3J_{H,H}$ = 2.9, 0.8 Hz, 1H, 3'-H), 4.65 (br s, 1H, OH), 4.05 (br s, 1H, OH), 3.80 (m, 4H, 2x1''-H, 1-H, 2-H), 3.53 (dd, $^2J_{H,H}$ = 11.3, $^3J_{H,H}$ = 6.9 Hz, 1H, 2-H), 3.25 (dddd, $^3J_{H,H}$ = 11.5, 4.0, 4.0, 0.8 Hz, 1H, 4'-H), 3.02 (ddd, $^3J_{H,H}$ = 10.6, 4.0, 0.8 Hz, 1H, 1'-H), 2.18 (br s, 1H, OH); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 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'); 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): To a stirred solution of triol **20** (240 mg, 1.66 mmol) in acetone (36 mL) were added, under argon atmosphere, anhydrous sodium sulfate (6.70 g, 47.20 mmol), anhydrous copper sulfate (2.50 g, 15.68 mmol) and one drop of HCl conc. After being stirred for 4 d at rt, the reaction was quenched with by the slow addition of 30% NH_3 and filtered through a Celite pad. The solvent was evaporated under reduced pressure without heating (because the product is volatile), and the crude material was purified by column chromatography over alumina (from hexane/diethyl ether 3:1 to diethyl eter) to furnish **17** (261 mg, 1.41 mmol, 85% yield) as a colorless oil: $[\alpha]_D$ = +16.3 (*c* = 0.98, $CHCl_3$); IR (ATR): υ = 3452 (br), 1370, 1212, 1150, 1058, 1019, 846, 745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 6.09 (dd, $^3J_{H,H}$ = 2.9, 1.1 Hz, 1H, 2'-H), 5.93 (ddd, $^3J_{H,H}$ = 2.9, 0.9, $^4J_{H,H}$ = 0.4 Hz, 1H, 3'-H), 4.18 (ddd, $^3J_{H,H}$ = 10.4, 6.0, 6.0 Hz, 1H, 4''-H), 4.11 (dd, $^2J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.0 Hz, 1H, 5''-H), 3.71 (m, 3H, 2x1-H, 5''-H), 3.45 (dd, $^3J_{H,H}$ = 9.1, 4.1 Hz, 1H, OH), 3.26 (m, 1H, 1'-H), 3.02 (ddd, $^3J_{H,H}$ = 10.4, 4.1, 0.9 Hz, 1H, 4'-H), 1.43 (s, 3H, C*H*$_3$-C-2''), 1.37 (s, 3H, C*H*$_3$-C-2''); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 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, *C*H$_3$-C-2''), 25.6 (CH_3, *C*H$_3$-C-2''); 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): To a solution of PPh_3 (243 mg, 0.88 mmol) in dry THF (5.5 mL), di-*tert*-butyl azodicarboxylate (203 mg, 0.88 mmol) was added and the solution was allowed to stir at rt 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 over the initial solution and the mixture was heated to reflux temperature. After 2 h, the mixture was allowed to cool to rt. Evaporation of the solvent and purification by column chromatography (from hexane-diethyl ether 2:1 to hexane-diethyl ether 1:1) afforded **21** (208 mg, 0.32 mmol, 73% yield) as a white foam: $[\alpha]_D$ = +37.0 (*c* = 0.87, $CHCl_3$); IR (ATR): υ = 2931, 1746, 1698, 1653, 1429, 1368, 1239, 1154, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.84 (m, 2H, Ar), 7.65-7.54 (m, 5H, Ar), 7.49-7.32 (m, 9H, Ar/H-6), 4.67 (ddd, $^3J_{H,H}$ = 10.8, 6.8, 6.8 Hz, 1H, 4'''-H), 4.39 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.5 Hz, 1H, 5'''-H), 4.18 (ddd, $^3J_{H,H}$ = 7.5, 7.5, 7.5 Hz, 1H, 3''-H), 3.95 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 6.8 Hz, 1H, 1'-H), 3.82 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 3.67 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.8 Hz, 1H, 5'''-H), 2.66 (dddd, $^3J_{H,H}$ = 10.8, 7.5, 7.5, 3.4 Hz, 1H, 2''H), 2.19-2.07 (m, 1H, 1''-H), 2.00-1.86 (m, 2H, 4''-H), 1.91 (d, $^4J_{H,H}$ = 1.0 Hz, 3H, C*H*$_3$-C5), 1.42 (s, 3H, C*H*$_3$-C2'''), 1.40 (s, 3H, C*H*$_3$-C2'''), 1.04 (s, 9H, (C*H*$_3$)$_3$C); ^{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 (2xCH, Ph), 135.5 (2xCH, Ph), 134.9 (C, Bz), 133.5 (C, Ph), 133.1 (C, Ph), 131.9 (CH, Bz), 130.4 (2xCH, Bz), 130.1 (CH, Ph), 130.0 (CH, Ph), 129.2 (2xCH, Bz), 127.9 (2xCH, Ph), 127.8 (2xCH, 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 (4xCH_3, (*C*H$_3$)$_3$C/*C*H$_3$-C2'''), 25.7 (CH_3, *C*H$_3$-C2'''), 19.0 (C, (CH_3)$_3$*C*), 12.4 (CH_3, *C*H$_3$-C5); 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): To a solution of PPh_3 (97 mg, 0.37 mmol) in dry THF (2.5 mL), DBAD (85 mg, 0.37 mmol) was added and the solution was allowed to stir at rt 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 over the initial solution and the mixture was heated to reflux temperature. After 5h, the mixture was allowed to cool to rt. Evaporation of the solvent and purification by column chromatography (from hexane-diethyl ether 5:1 to hexane-diethyl ether 1:1) afforded **22** (76 mg, 0.12 mmol, 62% yield) as a white foam: $[\alpha]_D$ = +43.7 (*c* = 0.93, $CHCl_3$); IR (ATR): ν = 2929, 1751, 1712, 1666, 1449, 1237, 1156 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.91-7.79 (m, 2H, Ar), 7.83 (d, $^3J_{H,H}$ = 6.1 Hz, 1H, 6-H), 7.69-7.52 (m, 5H, Ar), 7.52-7.30 (m, 8H, Ar), 4.67 (ddd, $^3J_{H,H}$ = 10.9, 6.5, 6.5 Hz, 1H, 4'''-H), 4.42 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 6.5 Hz, 1H, 5'''-H), 4.18 (ddd, $^3J_{H,H}$ = 7.5, 7.5, 7.5 Hz, 1H, 3''-H), 3.97 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.2 Hz, 1H, 1'-H), 3.75 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 7.4 Hz, 1H, 1'-H), 3.71 (dd, $^2J_{H,H}$ = 8.5, $^3J_{H,H}$ = 6.5 Hz, 1H, 5'''-H), 2.69 (dddd, $^3J_{H,H}$ = 10.9, 7.5, 7.5, $^4J_{H,H}$ = 3.7 Hz, 1H, 2''H), 2.18-2.02 (m, 1H, 1''-H), 1.99-1.79 (m, 2H, 4''-H), 1.43 (s, 6H, 2xC*H*$_3$-C2'''), 1.05 (s, 9H, (C*H*$_3$)$_3$C); ^{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, 2xCH, Ph), 135.5 (s, 2xCH, Ph), 135.4 (s,

C, Bz), 133.4 (s, C, Ph), 133.0 (s, C, Ph), 131.3 (s, CH, Bz), 130.6 (s, 2xCH, 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, 2xCH, Bz), 128.0 (s, 2xCH, Ph), 127.9 (s, 2xCH, 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, 3xCH_3, (CH_3)$_3$C), 26.9 (s, CH_3, *C*H_3-C2'''), 25.7 (s, CH_3, *C*H_3-C2'''), 19.0 (s, C, (CH_3)$_3$*C*); ^{19}F NMR (235 MHz, $CDCl_3$): δ = -167.3 (d, $J_{F,6}$ = 6.1 Hz); 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 3 mL of a 33% $MeNH_2$ solution in EtOH. The solution was stirred for 30 min at rt. Then, the solvent was evaporated under reduced pressure and the crude was purified by column chromatography (hexane-EtOAc 1:1) to provide **23** (78 mg, 0.14 mmol, 80% yield) as a white foam: $[\alpha]_D$ = +40.6 (*c* = 0.42, $CHCl_3$); IR (ATR): ν = 2930, 2857, 1672, 1462, 1427, 1369, 1154, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.97 (br s, 1H, NH), 7.61-7.55 (m, 4H, Ph), 7.47-7.33 (m, 6H, Ph), 7.23 (q, $^4J_{H,H}$ = 1.0 Hz, 1H, 6-H), 4.67 (ddd, $^3J_{H,H}$ = 10.8, 6.5, 6.5 Hz, 1H, 4'''-H), 4.39 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.5 Hz, 1H, 5'''-H), 4.17 (ddd, $^3J_{H,H}$ = 7.3, 7.3, 7.3 Hz, 1H, 3''-H), 3.89 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 3.78 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 6.8 Hz, 1H, 1'-H), 3.65 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.5 Hz, 1H, 5'''-H), 2.63 (dddd, $^3J_{H,H}$ = 10.8, 7.3, 7.3, $^4J_{H,H}$ = 3.6 Hz, 1H, 2''-H), 2.17-2.06 (m, 1H, 1''-H), 2.00-1.88 (m, 2H, 4''-H), 1.87 (d, $^4J_{H,H}$ = 1.0 Hz, 3H, C*H*$_3$-C5), 1.41 (s, 3H, C*H*$_3$-C2'''), 1.38 (s, 3H, C*H*$_3$-C2'''), 1.05 (s, 9H, (C*H*$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5 (C=O, C4), 151.1 (C=O, C2), 141.5 (CH, C6), 135.8 (2xCH, Ph), 135.5 (2xCH, Ph), 133.5 (C, Ph), 133.2 (C, Ph), 130.1 (CH, Ph), 130.0 (CH, Ph), 127.9 (2xCH, Ph), 127.8 (2xCH, 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 (3xCH_3, (*C*H$_3$)$_3$C), 27.0 (CH_3, *C*H_3-C2'''), 25.7 (CH_3, *C*H_3-C2'''), 19.0 (C, (CH_3)$_3$*C*), 12.4 (CH_3, *C*H_3-C5); 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 to reflux temperature and it was allowed to stir for 5 h. Then, the solution was allowed to cool to room temperature and the solvent was evaporated. The crude was purified by filtration through DOWEX 1x8 resin and column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **7-T** (32 mg, 0.12 mmol, 84% yield) as a white solid: mp 45-47 °C (MeOH); $[\alpha]_D$ = -49.1 (*c* = 1.06, MeOH); IR (ATR): ν = 3100-3500, 2963, 1655, 1260 cm^{-1}; ^{1}H NMR (400 MHz, MeOD): δ = 7.48 (d, $^4J_{H,H}$ = 1.2 Hz, 1H, 6-H), 4.24 (ddd, $^3J_{H,H}$ = 6.5, 6.5, 6.5 Hz, 1H, 3''-H), 4.15 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 5.2 Hz, 1H, 1'-H), 4.12-4.15 (m, 1H, 1'''-H), 4.05 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 10.4 Hz, 1H, 1'-H), 3.78 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 3.7 Hz, 1H, 2'''-H), 3.46 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 6.4 Hz, 1H, 2'''-H), 2.65-2.55 (m, 1H, 2''-H), 2.55-2.45 (m, 1H, 1''-H), 2.33 (dddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 6.5, 6.5, $^4J_{H,H}$ = 2.5 Hz, 1H, 4''-H), 1.90 (ddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 7.8, 6.5 Hz, 1H, 4''-H), 1.86 (d, $^4J_{H,H}$ = 1.2 Hz, 3H, C*H*$_3$-C5); ^{13}C NMR (100 MHz, MeOD): δ = 166.9 (C=O, C-4), 153.1 (C=O, C2), 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-C5); 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 2.5 mL of a 33% $MeNH_2$ solution in EtOH. The solution was stirred for 30 min at rt. Afterwards, the solvent was evaporated under reduced pressure and the crude was purified by column chromatography (hexane-EtOAc 1:1) to provide **24** (63 mg, 0.11 mmol, 95% yield) as a yellow foam; $[\alpha]_D$ = +52.0 (*c* = 1.23, $CHCl_3$); IR (ATR): ν = 3070, 2931, 2857, 1688, 1662, 1372, 1238, 1155, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.47 (d, $^4J_{H,H}$ = 5.2 Hz, 1H, N*H*), 7.70 (d, $^3J_{H,H}$ = 5.2 Hz, 1H, 6-H), 7.60-7.55 (m, 4H, Ph), 7.47-7.34 (m, 6H, Ph), 4.66 (ddd, $^3J_{H,H}$ = 10.9, 6.5, 6.5 Hz, 1H, 4'''-H), 4.41 (dd, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 6.5, 1H, 5'''-H), 4.18 (ddd, $^3J_{H,H}$ = 8.5, 7.3, 7.3 Hz, 1H, 3''-H), 3.92 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.5 Hz, 1H, 1'-H), 3.71 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 8.0 Hz, 1H, 1'-H), 3.69 (dd, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 6.5 Hz, 1H, 5'''-H), 2.65 (dddd, $^3J_{H,H}$ = 10.9, 7.3, 7.3, $^4J_{H,H}$ = 3.7 Hz, 1H, 2''-H), 2.16-2.04 (m, 1H, 1''-H), 1.97 (dddd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 7.3, 7.3, $^4J_{H,H}$ = 3.7 Hz, 1H, 4''-H), 1.87 (ddd, $^2J_{H,H}$ = 10.8, $^3J_{H,H}$ = 10.8, 8.5 Hz, 1H, 4''-H), 1.42 (s, 3H, C*H*$_3$-C2'''), 1.40 (s, 3H, C*H*$_3$-C2'''), 1.05 (s, 9H, (C*H*$_3$)$_3$C); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4 (d, $J_{C,F}$=26.0 Hz, C=O, C4), 149.8 (s, C=O, C-2), 139.9 (d, $J_{C,F}$=235.5 Hz, C, C-5), 135.7 (s, 2xCH, Ph), 135.5 (s, 2xCH, 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, 2xCH, Ph), 127.9 (s, 2xCH, 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, 3xCH_3, (*C*H$_3$)$_3$C), 26.8 (s, CH_3, *C*H_3-C2'''), 25.7 (s, CH_3, *C*H_3-C2'''), 19.0 (s, C, (CH_3)$_3$*C*); ^{19}F NMR (376 MHz, $CDCl_3$): δ = -167.7 (t, $J_{F,NH}$ = 5.2 Hz, $J_{F,6}$ = 5.2 Hz); 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 to reflux temperature and it was allowed to stir overnight. Then, the solution was allowed to cool to rt and the solvent was evaporated. The crude was purified by filtration through DOWEX 1x8 resin and column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **7-U^F** (20 mg, 0.07 mmol, 67% yield) as a yellow oil: $[\alpha]_D$ = -36.2 (*c* = 0.85, MeOH); IR (ATR): ν = 3500-3100, 2939, 1657, 1371, 1237 cm^{-1}; ^{1}H NMR (400 MHz, MeOD): δ = 7.89 (d, $^3J_{H,H}$ = 6.3 Hz, 1H, 6-H), 4.23 (ddd, $^3J_{H,H}$ = 6.6, 6.6, 6.6 Hz, 1H, 3''-H), 4.13 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 5.6 Hz, 1H, 1'-H), 4.14-4.07 (m, 1H, 1'''-H), 4.03 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 9.8 Hz, 1H, 1'-H), 3.78 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 3.7 Hz, 1H, 2'''-H), 3.45 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 6.3 Hz, 1H, 2'''-H), 2.59 (dddd, $^3J_{H,H}$ = 11.0, 8.8, 6.6, $^4J_{H,H}$ = 2.4 Hz, 1H, 2''-H), 2.55-2.45 (m, 1H, 1''-H), 2.37 (dddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 6.6, 6.6, $^4J_{H,H}$ = 2.4 Hz, 1H, 4''-H), 1.89 (ddd, $^2J_{H,H}$ = 11.4, $^3J_{H,H}$ = 8.4, 6.6 Hz, 1H, 4''-H); ^{13}C NMR (100 MHz, MeOD): δ = 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''); ^{19}F NMR (376 MHz, MeOD): δ = -171.0 (d, $J_{F,6}$ = 6.3 Hz); 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 2 mL of a 1:1 mixture of THF/H_2O. 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 allowed to stir at rt. 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 was allowed to stir for 2 h, when it was quenched by the addition of saturated NH_4Cl solution. When the bubbling ceased, some drops of concentrated NH_3 were added and the mixture was evaporated to dryness and purified by column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **25-T** (16 mg, 0.07 mmol, 73% yield) as a white solid: mp 96-98 °C (MeOH); IR (ATR): ν = 3461, 3354, 2915, 1668, 1470, 1420, 1348, 1226, 1102, 1075 cm^{-1}; ^{1}H NMR (360 MHz, MeOD): δ = 7.45 (q, $^4J_{H,H}$ = 1.2 Hz, 1H, 6-H), 3.71 (d, $^3J_{H,H}$ = 10.5 Hz, 2H, 1'-H), 3.69-3.57 (m, 4H, 4'-H), 2.10 (dq, $^3J_{H,H}$ = 10.5, 6.7 Hz, 1H, 2'-H), 1.88 (d, $^4J_{H,H}$ = 1.2 Hz, 3H, C*H*$_3$-C5), 1.56 (m, 4H, 3'-H); ^{13}C NMR (90 MHz, MeOD): δ = 166.9 (C=O, C-4), 153.3 (C=O, C-2), 143.5 (CH, C-6), 111.0 (C, C-5), 60.4

(2xCH$_2$, C-4'), 53.1 (CH$_2$, C-1'), 35.1 (2xCH$_2$, C-3'), 33.3 (CH, C-2'), 12.2 (CH$_3$, *C*H$_3$-C5); 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): To a solution of **23** (205 mg, 0.31 mmol) in THF (5.5 mL), a 1 M solution of TBAF in THF (630 µL, 0.63 mmol) was added. After 2 h, the mixture was evaporated to dryness and the crude was purified by column chromatography (from hexane-EtOAc 1:1 to EtOAc) to afford a crude which was dissolved in a 33% $MeNH_2$ solution in EtOH (6.5 mL). The solution was stirred for 2 h at rt. Then, the solvent was evaporated under reduced pressure and the crude was purified by column chromatography (from hexane-EtOAc 1:1 to EtOAc) to give **26** (96 mg, 0.31 mmol, 99% yield) as a white foam: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.38-9.25 (m, 1H, NH), 7.25 (q, $^4J_{H,H}$ = 0.9 Hz, 1H, 6-H), 4.58 (ddd, $^3J_{H,H}$ = 10.6, 6.8, 6.6 Hz, 1H, 4'''-H), 4.32-4.19 (m, 2H, 5'''-H/3''-H), 4.02 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 7.3 Hz, 1H, 1'-H), 3.81 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 6.5 Hz, 1H, 1'-H), 3.60 (dd, $^2J_{H,H}$ = 8.2, $^3J_{H,H}$ = 7.2 Hz, 1H, 5'''-H), 2.65 (dddd, $^3J_{H,H}$ = 10.6, 7.2, 7.2 Hz, $^4J_{H,H}$ = 3.6 Hz, 1H, 2''-H), 2.52-2.26 (m, 3H, 1''-H/4''-H/OH), 1.97 (dddd, $^2J_{H,H}$ = 8.6, $^3J_{H,H}$ = 8.6, 8.6 Hz, 1H, 4''-H), 1.88 (d, $^4J_{H,H}$ = 0.9 Hz, 3H, C*H*$_3$-C5), 1.39 (s, 3H, C*H*$_3$-C2'''), 1.37 (s, 3H, C*H*$_3$-C2''').

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 rt. Then, a solution of **26** (97 mg, 0.31 mmol) in dry THF (3 mL) was added dropwise over the ^{t}BuOK suspension. The mixture was allowed to stir for 30 min at rt. At the same time, BnBr (114 µL, 0.94 mmol) was added dropwise over a suspension of NaI (142 mg, 0.94 mmol) in dry THF (2 mL) and the mixture was allowed to stir for 30 min at rt. At this point, the BnI solution was added dropwise over the initial solution and the mixture was allowed to stir for 30 min. The reaction was quenched by the addition of saturated solution of NH_4Cl. The crude was diluted with EtOAc and the layers were separated. The aqueous layer was extracted with EtOAc, and the organic extracts were washed with saturated solution of $NaHCO_3$ and brine. The organic layer was then dried over $MgSO_4$ and evaporated to dryness. Purification of the crude by column chromatography (hexane-EtOAc 1:1) provided **27** (97 mg, 0.24 mmol, 78% yield) as a white solid: mp 156-158 °C (hexane-EtOAc); $[\alpha]_D$ = +52.4 (*c* = 0.96, $CHCl_3$); IR (ATR): ν = 3205, 2930, 1681, 1456, 1373, 1323, 1255, 1158, 1111, 1050 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (br s, 1H, N*H*), 7.36-7.24 (m, 6H, 6-H/Ph), 4.58 (ddd, $^3J_{H,H}$ = 10.7, 6.8, 6.8 Hz, 1H, 4'''-H), 4.43 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, C*H*$_2$-Ph), 4.31 (d, $^2J_{H,H}$ = 12.0 Hz, 1H, C*H*$_2$-Ph), 4.27 (dd, $^2J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.8 Hz, 1H, 5'''-H), 3.97 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 6.8 Hz, 1H, 1'-H), 3.95 (ddd, $^3J_{H,H}$ = 7.1, 7.1, 7.1 Hz, 1H, 3''-H), 3.85 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 6.8 Hz, 1H, 1'-H), 3.61 (dd, $^2J_{H,H}$ = 7.9, $^3J_{H,H}$ = 6.8 Hz, 1H, 5'''-H), 2.72 (dddd, $^3J_{H,H}$ = 10.7, 7.4, 7.1, $^4J_{H,H}$ = 3.2 Hz, 1H, 2''-H), 2.47-2.32 (m, 2H, 1''-H/4''-H), 1.98-1.89 (m, 1H, 4''-H), 1.90 (d, $^4J_{H,H}$ = 1.2 Hz, 3H, C*H*$_3$-C5), 1.38 (s, 6H, 2xC*H*$_3$-C2'''); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0 (C=O, C-4), 151.0 (C=O, C-2), 141.5 (CH, C-6), 138.1 (C, Ph), 128.6 (2xCH, Ph), 127.9 (CH, Ph), 127.5 (2xCH, Ph), 109.8 (C, C-5), 108.4 (C, C-2'''), 72.9 (CH, C-4'''), 70.6 (CH$_2$, *C*H$_2$-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$_3$, *C*H$_3$-C2'''), 25.8 (CH$_3$, *C*H$_3$-C2'''), 12.4 (CH$_3$, *C*H$_3$-C-5); 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): To a solution of **27** (78 mg, 0.19 mmol) in MeOH (8 mL), *p*-toluenesulfonic acid (36 mg, 0.19 mmol) was added. The solution was allowed to stir for 4 h at rt. Then, the crude was evaporated to dryness, filtered through DOWEX 1x8 resin and purified by column chromatography (from EtOAc to EtOAc-MeOH 9:1) to afford **28** (63 mg, 0.17 mmol, 90% yield) as a white solid: mp 66-68 °C (MeOH); $[\alpha]_D$ = -36.4 (*c* = 1.21, MeOH); IR (ATR): ν = 3500-3100, 2923, 1660, 1454, 1347, 1209, 1139 cm^{-1}; ^{1}H NMR (400 MHz, MeOD): δ = 7.39 (q, $^4J_{H,H}$ = 1.0 Hz, 1H, 6-H), 7.36-7.22 (m, 5H, Ph), 4.52 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, C*H*$_2$-Ph), 4.31 (d, $^2J_{H,H}$ = 11.8 Hz, 1H, C*H*$_2$-Ph), 4.19-4.10 (m, 3H, 2x1'-H/1'''-H), 4.06 (ddd, $^3J_{H,H}$ = 11.8, 7.4, 2.6 Hz, 1H, 3''-H), 3.81 (dd, $^2J_{H,H}$ = 11.3, $^3J_{H,H}$ = 3.0 Hz, 1H, 2'''-H), 3.43 (dd, $^2J_{H,H}$ = 11.3, $^3J_{H,H}$ = 6.5 Hz, 1H, 2'''-H), 2.74 (ddddd, $^3J_{H,H}$ = 10.5, 7.4, 7.2, $^4J_{H,H}$ = 2.2, 1.2 Hz, 1H, 2''-H), 2.62-2.50 (m, 1H, 1''-H), 2.29-2.20 (m, 1H, 4''-H), 1.98 (dddd, $^2J_{H,H}$ = 7.5, $^3J_{H,H}$ = 6.3, 2.6, $^4J_{H,H}$ = 1.2 Hz, 1H, 4''-H), 1.85 (d, $^4J_{H,H}$ = 1.0 Hz, 1H, 6-H); ^{13}C NMR (100 MHz, MeOD): δ = 166.9 (C=O, C-4), 153.2 (C=O, C-2), 143.4 (CH, C-6), 139.7 (C, Ph), 129.4 (2xCH, Ph), 128.8 (2xCH, 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$_3$-C5); 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 9 mL of a 1:1 mixture of THF/H_2O. 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 allowed to stir at rt. 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. Then, $NaBH_4$ (41 mg, 1.08 mmol) was added and the reaction was allowed to stir for 2 h, when it was quenched by the addition of saturated NH_4Cl solution. When the bubbling ceased, some drops of concentrated NH_3 were added and the mixture was evaporated to dryness and purified by column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **29** (56 mg, 0.17 mmol, 77% yield) as a white foam: $[\alpha]_D$ = -57.9 (*c* = 1.21, MeOH); IR (ATR): ν = 3500-3000, 2930, 2361, 1661, 1468, 1352, 1252, 1206 cm^{-1}; ^{1}H NMR (400 MHz, MeOD): δ = 7.47 (q, $^4J_{H,H}$ = 0.8 Hz, 1H, 6-H), 7.34-7.23 (m, 5H, Ph), 4.43 (s, 2H, C*H*$_2$-Ph), 4.06 (ddd, $^3J_{H,H}$ = 7.3, 7.3, 7.3 Hz, 1H, 3''-H), 4.00-3.91 (m, 3H, 2x 1'''-H/1'-H), 3.85 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 9.1 Hz, 1H, 1'-H), 2.86-2.74 (m, 1H, 2''-H), 2.45-2.35 (m, 1H, 1''-H), 2.35-2.25 (m, 1H, 4''-H), 2.00 (ddd, $^2J_{H,H}$ = 10.2, $^3J_{H,H}$ = 10.0, 7.5 Hz, 1H, 4''-H), 1.85 (d, $^4J_{H,H}$ = 0.8 Hz, 3H, C*H*$_3$-C5); ^{13}C NMR (100 MHz, MeOD): δ = 166.9 (C=O, C-4), 153.0 (C=O, C-2), 143.4 (CH, C-6), 139.6 (C, Ph), 129.4 (2xCH, Ph), 128.9 (2xCH, 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$_3$-C5); 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): To a solution of **29** (55 mg, 0.17 mmol) in MeOH (2 mL), Pd/C (9 mg) was added. The mixture was heated to reflux temperature and ammonium formate (129 mg, 2.04 mmol) was added in portions throughout the course of the reaction. After 6 h, the mixture was allowed to cool to rt and filtered through a Celite pad. Evaporation of the solvent afforded **11-T** (39 mg, 0.16 mmol, 98% yield) as a white solid: mp 164-166 °C (MeOH); $[\alpha]_D$ = -50.8 (*c* = 1.22, MeOH); IR (ATR): ν = 3500-3000, 2926, 1705, 1664, 1432, 1351, 1236, 1055 cm^{-1}; ^{1}H NMR (400 MHz, MeOD): δ = 7.48 (q, $^4J_{H,H}$ = 1.0 Hz, 1H, 6-H), 4.26 (ddd, $^3J_{H,H}$ = 7.6, 7.6, 7.6 Hz, 1H, 3''-H), 3.97 (d, $^3J_{H,H}$ = 7.4 Hz, 2H, 2x 1'''-H), 3.95 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 5.7 Hz, 1H, 1'-H), 3.85 (dd, $^2J_{H,H}$ = 13.8, $^3J_{H,H}$ = 8.8 Hz, 1H, 1'-H), 2.74-2.65 (m, 1H, 2''-H), 2.42-2.30 (m, 2H, 1''-H-/4''-H), 2.01-1.90 (m, 1H, 4''-H), 1.86 (d, $^4J_{H,H}$ = 1.0 Hz, 3H, C*H*$_3$-C5); ^{13}C NMR (100 MHz, MeOD): δ = 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$_3$-C5); 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 0 °C stirred suspension of alcohol **17** (147 mg, 0.80 mmol), *N3*-benzoylthymine (367 mg, 1.59 mmol) and triphenylphosphine (421 mg, 1.60 mmol) in anhydrous

THF (5.7 mL) under argon atmosphere. The mixture was allowed to warm to rt and stirred overnight. The organic solvent was removed under vacuum and the resulting oil was purified by repeated column chromatography (hexane-EtOAc from 10:1 to 1:1) to give **30** (201 mg, 0.51 mmol, 63% yield) as a colorless oil: $[\alpha]_D$ = +3.8 (*c* = 1.0, $CHCl_3$); IR (ATR): υ = 2984, 2930, 1745, 1696, 1648, 1436, 1238, 1062 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ = 7.91 (dd, *J* = 8.2, 1.2 Hz, 2H, H-Bz), 7.63 (m, 1H, H-Bz), 7.48 (t, *J* = 8.2 Hz, 2H, H-Bz), 7.26 (q, $^4J_{H,H}$ = 1.1 Hz, 1H, 6-H), 6.20 (dd, $^3J_{H,H}$ = 2.9, 0.9 Hz, 1H, 2''-H), 5.97 (d, $^3J_{H,H}$ = 2.9 Hz, 1H, 3''-H), 4.09 (m, 2H, 5'''-H, 4'''-H), 3.99 (m, 2H, 2x1'-H), 3.66 (m, 1H, 5'''-H), 3.33 (m, 1H, 1''-H), 3.07 (ddd, *J* = 9.8, 4.2, 0.8 Hz, 1H, 4''-H), 1.96 (d, $^4J_{H,H}$ = 1.1 Hz, 3H, C*H*$_3$-C-5), 1.41 (s, 3H, C*H*$_3$-C-2'''), 1.35 (s, 3H, C*H*$_3$-C-2'''); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 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); 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): To a solution of **30** (52 mg, 0.13 mmol) in MeOH (5.8 mL), *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol) was added and the resulting mixture was stirred for 28h at rt. After removal of the solvent, the residue was purified by column chromatography (from hexane-EtOAc 3:1 to EtOAc) to furnish **31** (30 mg, 0.08 mmol, 65% yield) as a colorless oil: $[\alpha]_D$ = -28.0 (*c* = 1.1, $CHCl_3$); IR (ATR): υ =3389 (br), 2923, 2853, 1741, 1691, 1639, 1259, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (dd, *J* = 8.3, 1.0 Hz, 2H, H-Bz), 7.63 (m, 1H, H-Bz), 7.48 (t, *J* = 8.3 Hz, 2H, H-Bz), 7.20 (d, $^4J_{H,H}$ = 0.8 Hz, 1H, 6-H), 6.14 (d, $^3J_{H,H}$ = 2.7 Hz, 1H, 2''-H), 5.99 (d, $^3J_{H,H}$ = 2.7 Hz, 1H, 3''-H), 4.21 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.9 Hz, 1H, 1'-H), 3.80 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 9.0 Hz, 1H, 1'-H), 3.65 (m, 2H, 2'''-H, 1'''-H), 3.41 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 7.2 Hz, 1H, 2'''-H), 3.28 (m, 1H, 1''-H), 2.98 (dd, *J* = 10.3, 4.1 Hz, 1H, 4''-H), 1.93 (d, $^4J_{H,H}$ = 0.8 Hz, 3H, C*H*$_3$-C-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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); 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 a 33% solution of $MeNH_2$ in EtOH (0.84 mL) was stirred overnight at rt. The volatiles were removed under vacuum, and the remaining crude was purified by flash column chromatography (CH_2Cl_2-MeOH from 50:1 to 20:1, containing 0.5% of NEt_3) to provide thymine nucleoside derivative **8-T** (18 mg, 0.07 mmol, 85% yield) as a white solid: mp 180-185 °C (MeOH); $[\alpha]_D$ = +249.9 (*c* = 0.6, MeOH); IR (ATR): υ = 3362 (br), 2961, 1660, 1260, 1092, 1021 cm^{-1}; ^1H NMR (360 MHz, CD_3OD): δ = 7.46 (q, $^4J_{H,H}$ = 1.1 Hz, 1H, 6-H), 6.17 (d, $^3J_{H,H}$ = 2.7 Hz, 1H, 2''-H), 6.12 (dd, $^3J_{H,H}$ = 2.7, 0.5 Hz, 1H, 3''-H), 4.19 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 5.1 Hz, 1H, 1'-H), 3.84 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 10.6 Hz, 1H, 1'-H), 3.65 (m, 2H, 1'''-H, 2'''-H), 3.49 (dd, $^2J_{H,H}$ = 11.8, $^3J_{H,H}$ = 6.6 Hz, 1H, 2'''-H), 3.31 (m, 1H, 1''-H), 3.03 (ddd, *J* = 9.7, 4.2, 0.5 Hz, 1H, 4''-H), 1.88 (d, $^4J_{H,H}$ = 1.1 Hz, 3H, C*H*$_3$-C-5); ^{13}C NMR (90 MHz, CD_3OD): δ = 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); 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*)- and (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 (32 and 33): To a stirred solution of **30** (34 mg, 0.09 mmol) in acetone-water 8:1 (0.9 mL), NMO (25 mg, 0.21 mmol) and OsO_4 (2.5 wt% in *t*-BuOH solution, 54 µL, $4.31x10^{-3}$ mmol) were added. After being stirred for 6 h at rt, the reaction was quenched by the addition of 10% $NaHSO_3$ (0.9 mL) and the mixture was allowed to stir for 30 min. Then, the aqueous phase was extracted with EtOAc (4 x 2 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the crude material by flash column chromatography (hexane-EtOAc from 1:1 to 1:6) yielded the diol **32** (13 mg, 0.03 mmol, 35% yield) and the corresponding diastereomer **33** (12 mg, 0.03 mmol, 32% yield), both as white foams.

32: $[\alpha]_D$ = +1.5 (*c* = 1.0, MeOH); IR (ATR): υ = 3392 (br), 2917, 2849, 1742, 1693, 1648, 1461, 1259, 1017 cm^{-1}; ^1H NMR (600 MHz, CD_3OD): δ = 7.96 (dd, *J* = 8.4, 1.2 Hz, 2H, H-Bz), 7.72 (m, *J* = 7.3, 1.2 Hz, 1H, H-Bz), 7.69 (q, $^4J_{H,H}$ = 1.1 Hz, 1H, 6-H), 7.56 (dd, *J* = 8.4, 7.3 Hz, 2H, H-Bz), 4.28 (dddd, *J* = 10.0, 10.0, 6.6, 6.6 Hz, 1H, 4'''-H), 4.11 (m, 3H, 1'-H, 2''-H, 5'''-H), 3.96 (m, 1H, 1'-H), 3.94 (m, 1H, 3''-H), 3.63 (dd, *J* = 8.1, 6.6 Hz, 1H, 5'''-H), 2.80 (dddd, *J* = 10.0, 10.0, 6.1, 6.1 Hz, 1H, 1''-H), 2.39 (dddd, *J* = 10.0, 10.0, 4.3, 0.8 Hz, 1H, 4''-H), 1.93 (d, $^4J_{H,H}$ = 1.1 Hz, 3H, C*H*$_3$-C-5), 1.39 (s, 3H, C*H*$_3$-C-2'''), 1.33 (s, 3H, C*H*$_3$-C-2'''); ^{13}C NMR (90 MHz, CD_3OD): δ = 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); HRMS (ESI^+): calcd. for $[C_{22}H_{26}N_2O_7+Na]^+$453.1632; found 453.1641.

33: $[\alpha]_D$ = -33.7 (*c* = 0.9, MeOH); IR (ATR): υ = 3426 (br), 2923, 1745, 1692, 1642, 1442, 1258, 1056 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 7.94 (d, *J* = 8.1 Hz, 2H, H-Bz), 7.75 (q, $^4J_{H,H}$ = 1.0 Hz, 1H, 6-H), 7.71 (m, 1H, H-Bz), 7.56 (dd, *J* = 8.1, 8.1 Hz, 2H, H-Bz), 4.69 (ddd, *J* = 13.0, 6.7, 6.7 Hz, 1H, 4'''-H), 4.34 (ddd, *J* = 5.5, 5.5, 2.5 Hz, 1H, 2''-H), 4.20 (m, 3H, 1'-H, 3''-H, 5'''-H), 4.07 (dd, $^2J_{H,H}$ = 14.1, $^3J_{H,H}$ = 9.5 Hz, 1H, 1'-H), 3.52 (dd, $^2J_{H,H}$ = 8.2, $^3J_{H,H}$ = 6.7 Hz, 1H, 5'''-H), 2.68 (m, 1H, 1''-H), 2.57 (m, 1H, 4''-H), 1.92 (d, $^4J_{H,H}$ = 1.0 Hz, 3H, C*H*$_3$-C-5), 1.35 (s, 3H, C*H*$_3$-C-2'''), 1.33 (s, 3H, C*H*$_3$-C-2'''); ^{13}C NMR (100 MHz, CD_3OD): δ = 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); 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): To a solution of diol **32** (22 mg, 0.05 mmol) in MeOH (2.5 mL), *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol) was added and the resulting mixture was stirred for 4 h at rt. Then, the reaction mixture was filtered through a basic anion exchange resin. The organic layer was concentrated under reduced pressure and 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 rt for 2 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 x 2.5 mL). The aqueous layer was concentrated under vacuum, and the resulting crude was then dissolved with MeOH and filtered through an acidic cation exchange resin. The organic solvent was evaporated under reduced pressure to obtain the thymine nucleoside derivative **9-T** (6 mg, 0.02 mmol, 40% yield) as a white foam: $[\alpha]_D$ = -17.7 (*c* = 0.9, MeOH); IR (ATR): υ = 3364 (br), 1677, 1475, 1260, 1091 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 7.48 (q, $^4J_{H,H}$ = 1.2 Hz, 1H, 6-H), 4.07 (m, 3H, 1'-H, 2''-H, 3''-H), 3.95 (dd, $^2J_{H,H}$ = 14.0, $^3J_{H,H}$ = 5.1 Hz, 1H, 1'-H), 3.75 (ddd, $^3J_{H,H}$ = 9.5, 6.9, 3.5 Hz, 1H, 1'''-H), 3.64 (dd, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 3.5 Hz, 1H, 2'''-H), 3.44 (dd, $^2J_{H,H}$ = 11.5, $^3J_{H,H}$ = 6.9 Hz, 1H, 2'''-H), 2.56 (m, 1H, 1''-H), 2.48 (m, 1H, 4''-H), 1.87 (d, $^4J_{H,H}$ = 1.2 Hz, 3H, C*H*$_3$-C-5); ^{13}C NMR (100 MHz, CD_3OD): δ = 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); 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): To a solution of diol **33** (25 mg, 0.06 mmol) 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 rt. Then, the reaction mixture was filtered through a basic anion exchange resin (Dowex 1X8 chloride form, 20-50 mesh). The organic layer was concentrated under reduced pressure and 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 rt 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 x 2.5 mL). The aqueous layer was concentrated under vacuum, and the resulting crude was then dissolved with MeOH and filtered through an acidic cation exchange resin (Dowex 50WX8 hydrogen form, 200-400 mesh). The organic solvent was evaporated under reduced pressure to afford the thymine nucleoside derivative **10-T** (9.5 mg, 0.03 mmol, 57% yield) as a white foam: $[\alpha]_D$ = -61.6 (*c* = 1.0, MeOH); IR (ATR): υ = 3370 (br), 1672, 1476, 1219, 1126 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 7.57 (q, $^4J_{H,H}$ = 1.1 Hz, 1H, 6-H), 4.25 (m, 2H, 1'-H, 3''-H), 4.19 (m, 2H, 1'-H, 2''-H), 4.06 (ddd, $^3J_{H,H}$ = 9.8, 6.1, 3.7 Hz, 1H, 1'''-H), 3.68 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 3.7 Hz, 1H, 2'''-H), 3.45 (dd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 6.1 Hz, 1H, 2'''-H), 2.80 (m, 1H, 1''-H), 2.40 (m, 1H, 4''-H), 1.86 (d, $^4J_{H,H}$ = 1.1 Hz, 3H, C*H*$_3$-C-5); ^{13}C NMR (100 MHz, CD_3OD): δ = 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, *C*H_3-C-5); 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): To a solution of PPh_3 (113 mg, 0.41 mmol) in dry THF (3 mL), DBAD (94 mg, 0.41 mmol) was added and the solution was allowed to stir at rt 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 over the initial solution and the mixture was allowed to stir overnight at rt. Then, the mixture was allowed to cool to rt. Evaporation of the solvent and purification by column chromatography (hexane-diethyl ether 2:1) afforded **34** (106 mg, 0.18 mmol, 87% yield) as a brownish oil: $[\alpha]_D$ = +27.9 (*c* = 0.98, $CHCl_3$); IR (ATR): ν = 3322, 2931, 1610, 1561, 1460, 1151, 1110, 1052 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.86 (s, 1H, 8-H), 7.62-7.52 (m, 4H, Ph), 7.47-7.31 (m, 6H, Ph), 5.13 (br s, 2H, NH_2), 4.74 (ddd, $^3J_{H,H}$ = 10.9, 6.4, 6.4 Hz, 1H, 4'''-H), 4.40 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.4 Hz, 1H, 5'''-H), 4.32 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.7 Hz, 1H, 1'-H), 4.20 (ddd, $^3J_{H,H}$ = 7.5, 7.5, 7.5 Hz, 1H, 3''-H), 4.08 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 3.67 (dd, $^2J_{H,H}$ = 8.4, $^3J_{H,H}$ = 6.4 Hz, 1H, 5'''-H), 2.66 (ddd, $^3J_{H,H}$ = 10.9, 7.5, 7.5 Hz, 1H, 2''-H), 2.41-2.23 (m, 1H, 1''-H), 1.97-1.87 (m, 2H, 2x 4''-H), 1.42 (s, 3H, C*H*$_3$-C2'''), 1.38 (s, 3H, C*H*$_3$-C2'''), 1.05 (s, 9H, (C*H*$_3$)$_3$C); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.0 (C, C-2), 153.9 (C, C-4), 151.1 (C, C-6), 143.3 (CH, C-8), 135.8 (2xCH, Ph), 135.5 (2xCH, Ph), 133.5 (C, Ph), 133.1 (C, Ph), 130.1 (CH, Ph), 130.1 (CH, Ph), 128.0 (2xCH, Ph), 127.9 (2xCH, 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 (3xCH_3, (*C*H$_3$)$_3$C), 27.0 (CH_3, *C*H_3-C2'''), 25.8 (CH_3, *C*H_3-C2'''), 19.0 (C, (CH$_3$)$_3$*C*); 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 to reflux temperature and it was allowed to stir overnight. Then, the solution was allowed to cool to rt and the solvent was evaporated. The crude was purified by filtration through DOWEX 1x8 resin and column chromatography (from EtOAc to EtOAc-MeOH 9:1) to give **7-G^{OMe}** (45 mg, 0.15 mmol, 82% yield) as a white solid: mp 155-157 °C (MeOH); $[\alpha]_D$ = -12.0 (*c* = 0.81, MeOH); IR (ATR): ν = 3500-3000, 2922, 2852, 2361, 1641, 1606, 1587, 1483, 1398, 1248, 1066 cm^{-1}; ^1H NMR (400 MHz, MeOD): δ = 7.85 (s, 1H, 8-H), 4.53 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 5.2 Hz, 1H, 1'-H), 4.38 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 9.8 Hz, 1H, 1'-H), 4.24 (ddd, $^3J_{H,H}$ = 6.7, 6.7, 1.3 Hz, 1H, 4''-H), 4.19 (ddd, $^3J_{H,H}$ = 10.0, 6.3, 3.8 Hz, 1H, 1'''-H), 4.04 (s, 3H, C*H*$_3$O-C6), 3.80 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 3.8 Hz, 1H, 2'''-H), 3.49 (dd, $^2J_{H,H}$ = 11.1, $^3J_{H,H}$ = 6.3 Hz, 1H, 2'''-H), 2.73-2.59 (m, 2H, 1''-H/2''-H), 2.28-2.20 (m, 1H, 3''-H), 1.86 (ddd, $^2J_{H,H}$ = 11.7, $^3J_{H,H}$ = 7.3, 6.7 Hz, 1H, 3''-H); ^{13}C NMR (100 MHz, MeOD): δ = 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-C6), 47.1 (CH_2, C-1'), 46.7 (CH, C-1''), 35.4 (CH_2, C-3''), 32.2 (CH, C-2''); 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 0 °C 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 argon atmosphere. The mixture was allowed to warm to rt and stirred overnight. The organic solvent was removed under vacuum and the resulting oil was purified by column chromatography (hexane-EtOAc from 10:1 to 1:1) to afford **35** (103 mg, 0.19 mmol, 60% yield) as a pale yellow solid: mp 44-47 °C ($CHCl_3$); $[\alpha]_D$ = +11.1 (*c* = 1.1, $CHCl_3$); IR (ATR): υ = 2961, 2921, 1723, 1369, 1260, 1094, 1020 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$): δ = 8.27 (s, 1H, 8-H), 6.16 (d, $^3J_{H,H}$ = 2.9 Hz, 1H, 2''-H), 6.00 (d, $^3J_{H,H}$ = 2.9 Hz, 1H, 3''-H), 4.59 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 6.5 Hz, 1H, 1'-H), 4.43 (dd, $^2J_{H,H}$ = 14.2, $^3J_{H,H}$ = 8.4 Hz, 1H, 1'-H), 4.15 (m, 2H, 5'''-H, 4'''-H), 3.69 (ddd, $^2J_{H,H}$ = 9.2, $^3J_{H,H}$ = 9.2, 6.5 Hz, 1H, 5'''-H), 3.49 (ddd, $^3J_{H,H}$ = 8.4, 6.5, 4.2 Hz, 1H, 1''-H), 3.10 (dd, $^3J_{H,H}$ = 9.2, 4.2 Hz, 1H, 4''-H), 1.44 (s, 18H, 2x(C*H*$_3$)$_3$CO), 1.40 (s, 3H, C*H*$_3$-C-2'''), 1.35 (s, 3H, C*H*$_3$-C-2'''); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 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 (2xC, (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 (6xCH_3, (*C*H$_3$)$_3$CO), 27.0 (CH_3, *C*H_3-C-2'''), 25.8 (CH_3, *C*H_3-C-2'''); 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):** To a solution of **35** (28 mg, 0.05 mmol) 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 rt. After removal of the solvent, the residue was purified by column chromatography (from hexane-EtOAc 1:1 to EtOAc-MeOH 9:1) to furnish **36** (18 mg, 0.04 mmol, 69% yield) as a white solid: mp 58-62 °C ($CHCl_3$); $[\alpha]_D$ = -3.2 (*c* = 0.9, $CHCl_3$); IR (ATR): υ = 2960, 2927, 1736, 1562, 1368, 1260, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.25 (s, 1H, 8-H), 6.15 (d, $^3J_{H,H}$ = 2.9 Hz, 1H, 2''-H), 6.07 (dd, $^3J_{H,H}$ = 2.9, 0.8 Hz, 1H, 3''-H), 4.67 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 7.2 Hz, 1H, 1'-H), 4.45 (dd, $^2J_{H,H}$ = 14.4, $^3J_{H,H}$ = 6.6 Hz, 1H, 1'-H), 3.74 (m, 1H, 2'''-H), 3.70 (m, 1H, 1'''-H), 3.54 (ddd, $^3J_{H,H}$ = 7.2, 6.6, 4.2 Hz, 1H, 1''-H), 3.49 (m, 1H, 2'''-H), 3.06 (ddd, $^3J_{H,H}$ = 10.3, 4.2, 0.8 Hz, 1H, 4''-H), 2.85 (br s, 1H, OH), 2.19 (br s, 1H, OH), 1.47 (s, 18H, 2x(C*H*$_3$)$_3$CO); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 (2xC, (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 (6xCH_3, (*C*H$_3$)$_3$CO); 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): To a stirred solution of **35** (32 mg, 0.06 mmol) in MeOH (1.4 mL), 1 N HCl (1.20 mL) was added. After being stirred at rt for 70 h, the reaction mixture was neutralized with NaOH (1 N) and added dropwise over diethyl ether (18 mL) and it was allowed to precipitate at 5 °C. The resulting solid was separated from the organic solvent by decantation and dried under vacuum to afford the **8-G** (15 mg, 0.05 mmol, 90% yield) as a pale yellow solid: mp >280 °C (MeOH); $[\alpha]_D$ = -126.4 (*c* = 1.1, MeOH); IR (ATR): υ = 3315 (br), 3175 (br), 2922, 1700, 1634, 1590, 1368, 1058 cm^{-1}; ^1H NMR (250 MHz, CD_3OD): δ = 9.08 (s, 1H, 8-H), 6.18 (m, 2H, 2''-H, 3''-H), 4.61 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 7.4 Hz, 1H, 1'-H), 4.37 (dd, $^2J_{H,H}$ = 13.9, $^3J_{H,H}$ = 8.1 Hz, 1H, 1'-H), 3.65 (m, 3H, 1'''-H, 2'''-H, 1''-H), 3.51 (dd, $^2J_{H,H}$ = 13.7, $^3J_{H,H}$ = 6.8 Hz, 1H, 2'''-H), 3.08 (dd, *J* = 10.0, 4.2 Hz, 1H, 4''-H); ^{13}C NMR (62.5 MHz, CD_3OD): δ =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''); 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 of the synthesis of intermediate **14**, crytallographic data, antiviral activity assays, computational methods information and ^1H 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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[1] (a) E. De Clercq, *Nat. Rev. Drug Discovery* **2002**, *1*, 13–25; (b) E. De Clercq, *Nat. Rev. Drug Discovery* **2007**, *6*, 1001–1018

[2] D. D. Richman, *Antiviral Res.* **2006**, *71*, 117-121.

[3] J. A. V. Coates, H. J. Inggall, B. A. Pearson, C. R. Penn, R. Storer, C. Williamson, J. M. Cameron, *Antiviral Res.* **1991**, *15*, 161-168.

[4] S. M. Daluge, S. S. Good, M. B. Faletto, W. H. Miller, M. H. St. Clair, L. R. Boone, M. Tisdale, N. R. Parry, J. E. Reardon, R. E. Dornsife, D. R. Averett, T. A. Krenitsky, *Antimicrob. Agents Chemother.* **1997**, *41*, 1082-1093.

[5] (a) W. A. Slusarchyk, M. G. Young, G. S. Bisacchi, D. R. Hockstein, R. Zahler, *Tetrahedron Lett.* **1989**, *30*, 6453-6456; (b) G. S. Bisacchi, A. Braitman, C. W. Cianci, J. M. Clark, A. K. Field, M. E. Hagen, D. R. Hockstein, M. F. Malley, T. Mitt, W. A. Slusarchyk, J. E. Sundeen, B. J. Terry, A. V. Tuomari, E. R. Weaver, M. G. Young, R. Zahler, *J. Med. Chem.* **1991**, *34*, 1415-1421.

[6] See for example: (a) F. Fernández, A. R. Hergueta, C. López, E. de Clercq, J. Balzarini, *Nucleosides, Nucleotides & Nucleic Acids* **2001**, *20*, 1129-1131; (b) L. Bondada, G. Gumina, R. Nair, X. H. Ning, R. F. Schinazi, C. K. Chu, *Org. Lett.* **2004**, *6*, 2531-2534; (c) Y. Marsac, A. Nourry, S. Legoupy, M. Pipelier, D. Dubreuil, A.-M. Aubertin, N. Bourgognon, R. Benhida, F. Huet, *Tetrahedron* **2005**, *61*, 7607-7612; (d) A. Rustullet, R. Alibés, P. de March, M. Figueredo, J. Font, *Org. Lett.* **2007**, *9*, 2827-2830.

[7] (a) C. Mathé, G. Gosselin, *Antiviral Res.* **2006**, *71*, 276-281; (b) S. Jessel, C. Meier, *Eur. J. Org. Chem.* **2011**, 1702-1713.

[8] H. Soudeyns, X. J. Yao, Q. Gao, B. Belleau, J. L. Kraus, B. Nghe Nguyen, B. Spira, M. A. Wainberg, *Antimicrob. Agents Chemother.* **1991**, *35*, 1386–1390.

[9] R. F. Schinazi, A. McMillan, D. Cannon, R. Mathis, R. M. Lioyd Jr., A. Peck, J. P. Sommadossi, M. St. Clair, J. Wilson, P.A. Furman, *Antimicrob. Agents Chemother.* **1992**, *36*, 2423-2431.

[10] (a) E. Cretton-Scott, X. J. Zhou, E. G. Bridges, B. Tennant, A. Juodawlkis, G. Gosselin, J. L. Imbach, C. Pierra, D. Dukhan, R. F. Schinazi, J. P. Sommadossi, M. Bryant, *Antivir. Ther.* **1999**, *4*, A124. (b) J. W. Kim, S. H. Park, S. G. Louie, *Ann. Pharmacothe.* **2006**, *40*, 472-478.

[11] G. Maury, *Antivir. Chem. Chemother.* **2000**, *11*, 165-190.

[12] M. Racamonde, R. Alibés, M. Figueredo, J. Font, P. de March, *J. Org. Chem.* **2008**, *73*, 5944-5952.

[13] S. Parés, R. Alibés, M. Figueredo, J. Font, T. Parella, *Eur. J. Org. Chem.* **2012**, 1404-1417.

[14] R. Alibés, J. L. Bourdelande, J. Font, *Tetrahedron: Asymmetry* **1991**, *2*, 1391-1402.

[15] R. Alibés, P. de March, M. Figueredo, J. Font, M. Racamonde, A. Rustullet, A. Álvarez-Larena, J. F. Piniella, T. Parella, *Tetrahedron Lett.* **2003**, *44*, 69-71.

[16] For recent reviews see: (a) R. Dembinski, *Eur. J. Org. Chem.* **2004**, 2763-2772; (b) T. Y. S. But, P. H. Toy, *Chem. Asian J.* **2007**, *2*, 1340-1355; (c) A. J. Reynolds, M. Kassiou, *Curr. Org. Chem.* **2009**, *13*, 1610-1632. (d) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551-2651.

[17] M. Frieden, M. Giraud, C. B. Reese, Q. Song, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2827-2832.

[18] (a) T. Maruyama, M. Ikejiri, K. Izawa, T. Onishi, In Fluorine in medicinal chemistry and chemical biology, Wiley-Blackwell: Chichester, UK, **2009**, Chapter 7, 165-198; (b) R.Filler, R. Saha, *Future Med. Chem.* **2009**, *1*, 777-791.

[19] J. I. Candela Lena, M. del R. Rico Ferreira, J. I. Martín Hernando, E. Altinel, S. Arseniyadis, *Tetrahedron Lett.* **2001**, *42*, 3179-3182.

[20] C. R. Schmid, , D. A. Bradley, *Synthesis* **1992**, 587-590.

[21] Z. Paryzec, H. Koenig, B. Tabaczka, *Synthesis* **2003**, 2023-2026.

[22] M. A. Fresneda, R. Alibés, J. Font, P. Bayón, M. Figueredo, *J. Org. Chem.* **2012**, *77*, 5030-5035.

[23] (a) K. B. Mullah, W. G. Bentrude, *J. Org. Chem.* **1991**, *56*, 7218-7224; (b) L. A. Paquette, A. L. Kahane, C. K. Seekamp, *J. Org. Chem.* **2004**, *69*, 5555-5562; (c) S. Zhou, J. Zemlicka, *Tetrahedron* **2005**, *61*, 7112-7116.

[24] C. McGuigan, K. Madela, M. Aljarah, A. Gilles, A. Brancale, N. Zonta, S. Chamberlain, J. Vernachio, J. Hutchins, A. Hall, B. Ames, E. Gorovits, B. Ganguly, A. Kolykhalov, J. Wang, J. Muhammad, J. M. Patti, G. Henson, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4850-4854.

[25] For a review on the functionalization of purines see: M. Legraverend, *Tetrahedron* **2008**, *64*, 8585-8603.

[26] (a) P. G. Reddy, D. Bao, W. Chang, B.-K. Chun, J. Du, D. Nagarathnam, S. Rachakonda, B. S. Ross, H.-R. Zhang, S. Bansal, C. L. Espiritu, M. Keilman, A. M. Lam, C. Niu, H. M. Steuer, P. A. Furman, M. J. Otto, M. J. Sofia, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7376-7380; (b) C. McGuigan, K. Madela, M. Aljarah, A. Gilles, S. K. Battina, , C. V. S. Ramamurty, C. S. Rao, J. Vernachio, J. Hutchins, A. Hall, A. Kolykhalov, G. Henson, S. Chamberlain, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6007-6012.

[27] Y. Tang, R. Muthyala, R.Vince, *Bioorg. Med. Chem.* **2006**, *14*, 5866-5875.

[28] (a) S. Dey, P. Garner, *J. Org. Chem.* **2000**, *65*, 7697-7699; (b) X.-Q.Yin, W.-K. Li, S. Schneller, *Tetrahedron Lett.* **2006**, *47*, 9187-9189.

[29] K. Barral, J. Courcambeck, G. Pèpe, J. Balzarini, J. Neyts, E. de Clercq, M. Camplo, *J. Med. Chem.* **2005**, *48*, 450-456.

[30] (a) M. F. Jacobsen, M. M. Knudsen, K. V. Gothelf, *J. Org. Chem.* **2006**, *71*, 9183-9190; (b) G. S. M. Sundaram, S. E. Harpstrite, J. L.-F. Kao, S. D. Collins, V. Sharma, *Org. Lett.* **2012**, *14*, 3568-3571.

[31] Detailed antiviral assay data for compounds **7-10, 25** and **36**, and related intermediates can be found in the Supplementary data.

[32] E. Sabini, S. Hazra, M. Konrad, A. Lavie, *J. Med. Chem.* **2007**, *50*, 3004-3014.

[33] (a) C. Meier, *Eur. J. Org. Chem.* **2006**, 1081-1102; A. S. Ray, K. Y. Hostetler, *Antiviral Res.* **2011**, *92*, 277-291.

[34] M. L. Verdonk, J. C. Cole, M. J. Hartshorn, C. W. Murray, R. D. Taylor, *Proteins* **2003**, *52*, 609-623.

[35] D. Deville-Bonne, C. El Amri, P. Meyer, Y. Chen, L. A. Agrofoglio, J. Janin, *Antiviral Res.* **2010**, *86*, 101-120.

[36] L. Toledo, L. Masgrau, J. D. Marechal, J. M. Lluch, A. González-Lafont, *J. Phys. Chem. B* **2010**, *114*, 7037-7046.

[37] J. N. Champness, M. S. Bennett, F. Wien, R. Visse, W. C. Summers, P. Herdewijn, E. de Clercq, T. Ostrowski, R. L. Jarvest, M. R. Sanderson, *Proteins* **1998**, *32*, 350–361.

[38] M. S. Bennett, F. Wien, J. N. Champness, T. Batuwangala, T. Rutherford, W. C. Summers, H. Sun, G. Wright, M. R. Sanderson, *FEBS Lett.* **1999**, *443*, 121-125.

[39] N. Sekulic, L. Shuvalova, O. Spangenberg, M. Konrad, A. Lavie, *J. Biol. Chem.* **2002**, *277*, 30236-30243.

[40] K. Wild, T. Bohner, G. Folkers, G. E. Schulz, *Protein Sci.*, 1997, **6**, 2097-2106.

[41] J. Cherfils, S. Moréra, I. Lascu, M. Véron, J. Janin, *Biochemistry* **1994**, ***33***, 9062–9069.

[42] S. Moréra, M. L. Lacombe, Y. Xu, G. LeBras, J. Janin, *Structure* **1995**, *3*, 1307–1314.

[43] B. Schneider, M. Babolat, Y. W. Xu, J. Janin, M. Véron, D. Deville-Bonne, *Eur. J. Biochem.* **2001**, *268*, 1964-1971.

[44] M. D. Eldridge, C. W. Murray, T. R. Auton, G. V. Paolini, R. P. Mee, *J. Comput.-Aided Mol. Des.* **1997**, *11*, 425–445.

[45] C. A. Baxter, C. W. Murray, D. E. Clark, D. R. Westhead, M. D. Eldridge, *Proteins* **1998**, *33*, 367–382.

[46] Marvin (version 5.4), 2010, ChemAxon (http://www.chemaxon.com).

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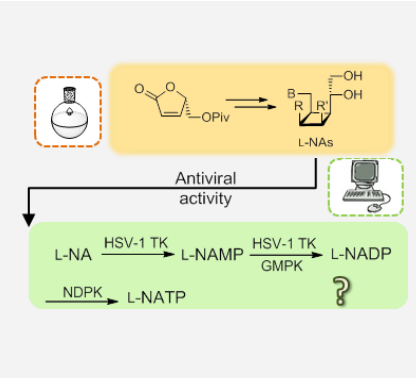

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