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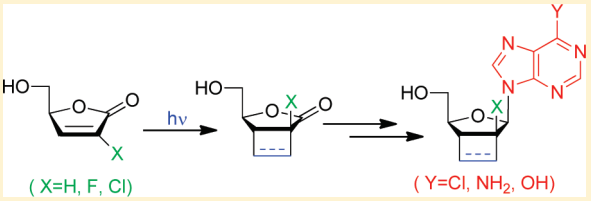
# Synthesis of Purine Nucleosides Built on a 3-Oxabicyclo[3.2.0]heptane Scaffold

Ramon Flores,[†] Albert Rustullet,[†] Ramon Alibés,*[,†] Angel Álvarez-Larena,[‡] Pedro de March,[†] Marta Figueredo,[†] and Josep Font[†]

[†]Departament de Química and [‡]Unitat de Crystal·lografia, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

Supporting Information

**ABSTRACT:** The photochemical [2 + 2] cycloaddition of chiral 3-chloro and 3-fluoro-5-hydroxymethyl-2(5*H*)-furanone to ethylene and acetylene has been studied. The effect of the halogen atom on the chemical yield and facial diastereoselectivity of the cycloaddition process has been evaluated. From the major anti cycloadducts, practical syntheses of several purine cyclobutane and cyclobutene-fused nucleosides containing a halogen atom have been developed. The anti-HIV activity of the new nucleoside analogues has been evaluated.




## INTRODUCTION

Over several decades, the search for more effective and less toxic antiviral agents against the human immunodeficiency virus (HIV) and hepatitis B virus (HBV) has been focused on 2′,3′-dideoxy nucleosides (ddNs). Some successful examples are 3′-azido-2′,3′-dideoxythymidine (AZT, zidovudine),[1] 2′,3′-dideoxyinosine (ddI, didanosine),[2] and 2′,3′-dideoxycytidine (ddC, zalcitabine) (Figure 1).[3] However, side effects, limited stability, and the emergence of drug-resistant mutants remain major drawbacks of these antiviral agents.[4] Consequently, there is a continuous demand for the identification of structurally new nucleoside derivatives with potent antiviral activity and low toxicity and also for new insights into the structure−activity relationship of these compounds.

The search for new active nucleoside analogues has been primarily focused on modification of the carbohydrate moiety. A structural feature that has often been beneficial for antiviral activity is a 2′,3′-unsaturation as in 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, stavudine).[5] Regarding the substituents of the ring, nucleoside analogues with a fluorinated sugar moiety have drawn increasing attention, with many of them showing a broad spectrum of antiviral and anticancer activities.[6] It is well-known that the introduction of fluorine atoms into an organic molecule often modifies the chemical, physical, and biological properties of the parent compound.[7]

Moreover, it has been found that the introduction of a fluorine atom into the 2′-position of nucleosides results in the stabilization of the glycosyl bond and confers distinctive biological activity.[8] This is a very interesting property, particularly for d2- and d4-purine nucleosides, since it is well established that they are unstable in acidic media, thus limiting their use as orally bioavailable drugs.[9] Accordingly, 2′-fluoro-2′,3′-dideoxy nucleosides have been prepared and evaluated as anti-HIV agents and many of them revealed as potent analogues,[10] among which is

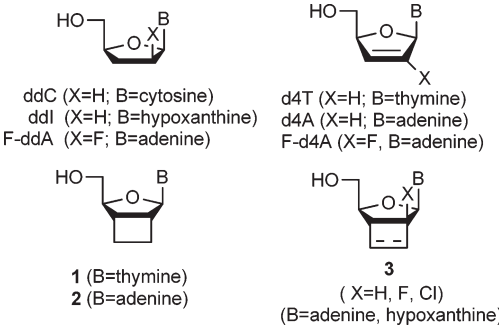



**Figure 1.** 2′,3′-Dideoxynucleosides with recognized activity and novel bicyclic nucleosides built on a 3-oxabicyclo[3.2.0]heptane scaffold.

2′-β-fluoro-2′,3′-dideoxyadenosine (F-ddA, Lodenosine).[11] Different 2′-fluoro-2′,3′-unsaturated purine analogues have also been synthesized showing potent anti-HIV activity without significant cytotoxicity.[12]

On the other hand, it is well-known that the conformation and puckering of the glycon moiety of nucleosides play a critical role in modulating their biological activity.[13] Therefore, over the past few years, a considerable amount of work has been done in the synthesis of nucleoside derivatives with fixed sugar-ring puckering, which has provided useful information regarding the relationship between sugar ring conformation and biological activity.[14] In this regard, we have recently described the synthesis and conformational analysis of a novel class of nucleoside analogues, **1** and **2**, with the glycone moiety conformationally restricted by a two-carbon chain between positions 2′ and 3′, which substantially mimic the 2′,

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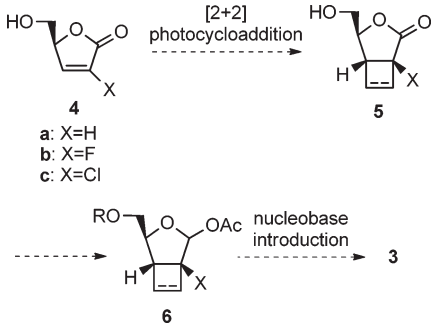
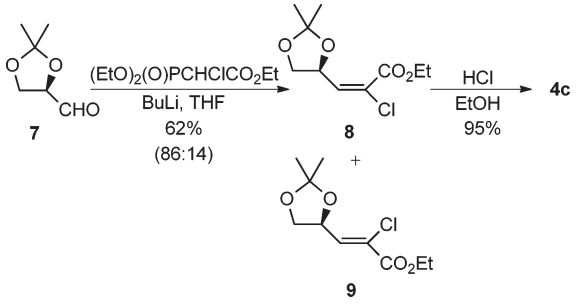
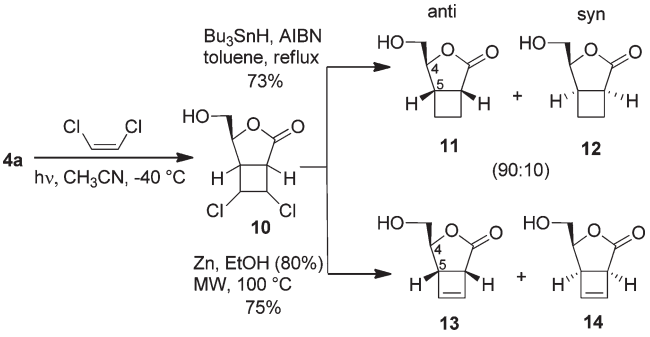
**Scheme 1. Synthetic Strategy to Purine Nucleosides Built on a 3-Oxabicyclo[3.2.0]heptane Scaffold**




**Scheme 2. Synthesis of the Chlorolactone 4c**




**Scheme 3. Preparation of 11 and 13**




3′-didehydro-2′,3′-dideoxynucleoside structure of the well-known antiviral agents d4T and d4A.[15]

Considering all these aspects, and in continuation of our efforts to synthesize nucleoside analogues built on a 3-oxabicyclo[3.2.0] heptane scaffold, we turned our attention to the elaboration of the hitherto unknown cyclobutane and cyclobutene purine D-nucleosides of type **3** (Figure 1) containing a heteroatom (such as fluorine or chlorine) at the 2′-position. Herein, we describe the synthesis and anti-HIV activity of such compounds.

## RESULTS AND DISCUSSION

Our synthetic plan (Scheme 1) involves the diastereoselective construction of the cyclobutane or cyclobutene ring through a [2 + 2] photochemical reaction of enantiopure 5-hydroxymethyl-2(5*H*)-furanone derivatives **4a**−**c**, the conversion of the cycloadducts **5** to the key intermediates **6**, and a subsequent introduction of the selected bases by a Vorbrüggen-type reaction.

Accordingly, our initial efforts focused on the preparation of the bicyclic compounds of type **5**. 2(5*H*)-Furanones **4a**[16] and **4b**[17] were synthesized following procedures described in the literature, while the 3-chloro-2(5*H*)-furanone **4c** was synthesized by a methodology similar to that used to prepare its fluoro analogue (Scheme 2). Thus, the Horner−Emmons reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde, **7**, with triethyl 2-chloro-2-phosphonoacetate and BuLi in dry THF afforded a chromatographically separable mixture of olefins **8** and **9** (86:14) in 62% yield. The use of other bases such as sodium hexamethyldisilylamide (NaHMDS) proved to be less effective for this transformation. Acid treatment of the major stereoisomer **8** delivered **4c** in 95% yield.

The cyclobutane derivative **11** has been efficiently prepared by our two-step protocol[18] consisting of the photochemical [2 + 2] cycloaddition of lactone **4a** with (*Z*)-1,2-dichloroethylene to afford a mixture of dichlorocycloadducts **10**, followed by a dihydrodehalogenation reaction of **10** by treatment with *n*-tributyltin hydride and AIBN in refluxing toluene. This protocol delivered a 90:10 mixture of the cyclobutanes **11** and **12** in 73% overall yield (Scheme 3).[15] Alternatively, treatment of the mixture of **10** with activated Zn in 80% EtOH in a sealed vessel at 100 °C, under microwave irradiation (microwave reactor, IR temperature monitoring), furnished a mixture of the cyclobutene diastereomers **13** and **14** in 90:10 ratio and 75% yield, wherefrom the major isomer **13** could be isolated by column chromatography in 65% yield. The structure of the products was assigned by 1D and 2D NMR spectroscopy. The value of the coupling constant between H-4 and H-5 is diagnostic for the anti/syn relative configuration of the cycloadducts. A small value of $J_{4,5}$ (1.7 Hz) is in agreement with a trans relationship between these two protons, whereas a larger value (4.3 Hz) indicates a cis relationship.[19]

Next, we turned our attention to the synthesis of the 3-oxabicyclo[3.2.0]heptane scaffold bearing a fluoride or chloride atom at the α-carbonyl position in which the presence of the halogen atom precludes the utilization of the above protocol. Therefore, we decided to prepare the halo derivatives by photochemical [2 + 2] cycloaddition of the corresponding 3-halo-2(5*H*)-furanones **4b** and **4c**[20] to ethylene and acetylene. So far, there have been limited reports on the photochemical behavior of α,β-unsaturated ketones or lactones containing a vinylic halogen atom,[21] and to the best of our knowledge, photochemical reactions of 3-halo-2(5*H*)-furanones with unsaturated substrates have not been reported yet. The influence of the α-halogen atom over the reactivity and stereoselectivity has been evaluated using as a control the photoreaction of lactone **4a** with ethylene and acetylene (Scheme 4). The results are summarized in Table 1.

First, we studied the photoreaction of lactones **4a**−**c** with ethylene. The photoreaction of lactone **4b** (entry 2) afforded an 81:19 mixture of the anti:syn isomers **15** and **16** from which the major isomer **15** was isolated in 62% yield. Thus, the presence of a vinylic fluorine atom enhanced both the yield and the facial selectivity compared to the results with lactone **4a** (entry 1).[15] In contrast, the photochemical reaction of chlorolactone **4c** (entry 3) furnished a 72:11:17 mixture of three isomers in 85% global yield. Purification by column chromatography allowed the separation of all three products, which were identified as the anti cycloadduct **17** (58%) and the two spirocyclopropane lactones **23** (8%) and **24** (13%) (Figure 2). No presence of the syn cycloadduct **18** was observed in the crude material.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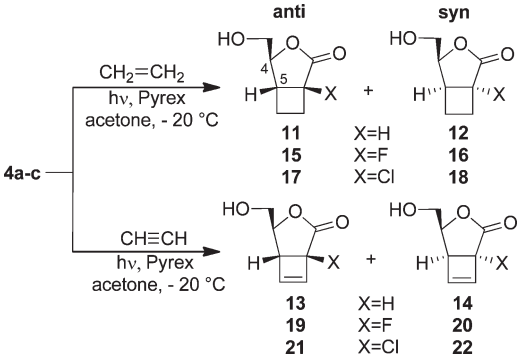
**Scheme 4. [2 + 2] Photochemical Cycloaddition of 4a−c to Ethylene and Acetylene**




The structure determination of the cyclopropane derivatives **23** and **24** was accomplished on the basis of their $^{1}H$ and $^{13}C$ NMR spectra with the help of 2D NMR experiments. For both compounds, the COSY experiments revealed two independent sets of signals, one of them containing four cyclopropane protons between 1.3 and 1.6 ppm (2 × H-1 and 2 × H-2) and the second containing the remaining four protons between 3.8 and 4.8 ppm (H-6, H-7, and 2 × H-8). The HMQC experiments showed the presence of a quaternary carbon atom at 28.6 ppm for **23** and 28.1 ppm for **24**, which were assigned to the spiranic position C-3. On the other hand, the HMBC experiments showed correlations between H-7 and C-1, C-2, C-3, and C-6 and between the cyclopropane protons H-1/H-2 and C-4. Finally, the configuration of the new stereogenic center C-7 was assigned considering the value of the coupling constant between H-6 and H-7, which is 5.0 Hz for **23**, indicating a cis disposition between H-6 and H-7, and 3.3 Hz for **24**, denoting a trans relationship.

The formation of the spirocyclopropyl derivatives **23** and **24** might be rationalized considering the postulated isomeric 1,4-biradical intermediates **I**−**IV** involved in the photochemical reaction (Scheme 5). Intermediates **I** and **II** would deliver the anti cycloadduct **17**, while **III** and **IV** direct to the syn isomer **18**. It has been suggested that the product distribution is controlled by the relative amount of the different isomeric 1,4-biradicals formed as well as by the extent to which each of them partitions between closure to the product and reversion to the precursors.[22,23] In this case, however, the 1,4-biradical intermediates **II** and **III** may evolve through a competitive pathway involving an intramolecular chlorine migration leading to the rearranged 1,3-biradical intermediates **II′** and **III′** that will eventually furnish the spirocyclopropyl lactones **23** and **24**. It is noteworthy to mention that, in this reaction, the formation of the syn cycloadduct **18** is not

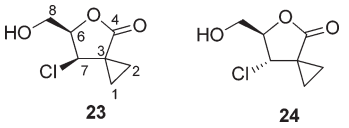
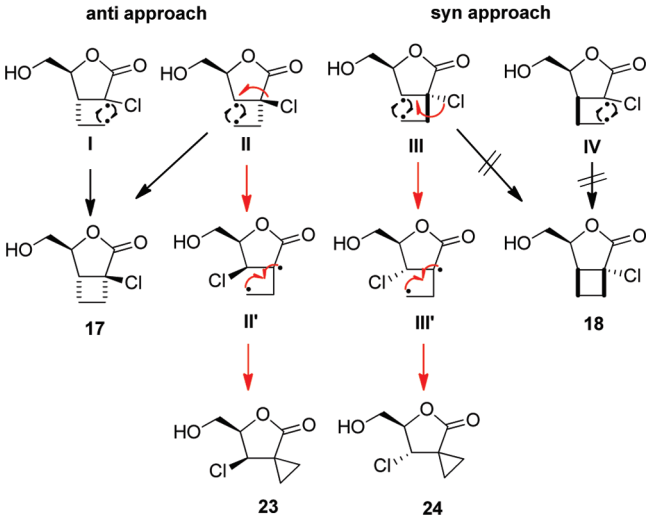



**Figure 2.** Spirocyclopropane lactones **23** and **24**.

**Scheme 5. Formation of the Spirocyclopropyl Lactones 23 and 24**




observed, meaning that the intermediate radical **III** leads exclusively to the spiro lactone **24.** Likely, due to the trans disposition of the hydroxymethyl chain and the chlorine atom in **III**, the intramolecular abstraction of the vicinal chlorine atom is favored over the cyclization process when compared with the analogous radical **II**, where a more sterically demanding situation may disfavor the chlorine migration.

Next, the [2 + 2] photocycloaddition of **4a**−**c** to acetylene was targeted to our attention (Table 1, entries 4−6). These photoreactions proceeded in much lower chemical yields. Thus, irradiation of an acetone solution of **4a** and acetylene for 5.3 h furnished a 65:35 mixture of the cyclobutene adducts **13** and **14** in 53% total yield (entry 4). The photoreaction of the fluorolactone **4b** (entry 5) afforded a complex crude material from which a 95:5 mixture of adducts **19** and **20** was isolated (28%), along with the unexpected tricyclic lactone **25** (15%, Figure 3). Likewise, the chlorolactone **4c** furnished the tricyclic lactone **26** (6%), besides the anti cycloadduct **21** (17%) (entry 6). In this case, the primary syn cycloadduct **22** was not even observed.

**Table 1. [2 + 2] Photocycloaddition of 2(5*H*)-Furanones 4a−c to Ethylene and Acetylene[a]**

| entry | lactone | X | unsaturated substrate | *t* | cycloadduct yield[b] (%) | anti:syn[c] (%) | other products[d] |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | H | ethylene | 5.5 h | 66 | 66:34 | |
| 2 | **4b** | F | ethylene | 3.5 h | 80 | 81:19 | |
| 3 | **4c** | Cl | ethylene | 4.5 h | 58 | 100:− | **23** (8%), **24** (13%) |
| 4 | **4a** | H | acetylene | 5.3 h | 53 | 65:35 | |
| 5 | **4b** | F | acetylene | 5.5 h | 28 | 95:5 | **25** (15%) |
| 6 | **4c** | Cl | acetylene | 4.5 h | 17 | 100:− | **26** (6%) |

[a] Substrates **4a**−**c** in acetone solutions saturated with ethylene or acetylene were irradiated through a Pyrex filter with a 125 W high-pressure mercury lamp at −20 °C. [b] Isolated yield of the mixture of stereoisomers after column chromatography. [c] Product ratio determined by GC and $^{1}H$ NMR. [d] Isolated yield after column chromatography.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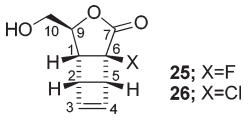
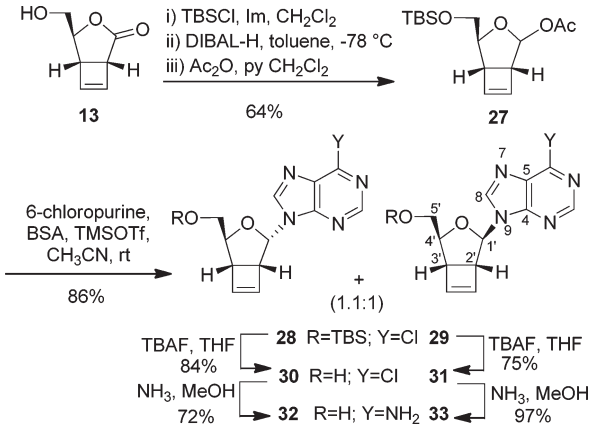



**Figure 3.** Tricyclic photoproducts.

**Scheme 6. Preparation of the Cyclobutene Adenine Analogues**



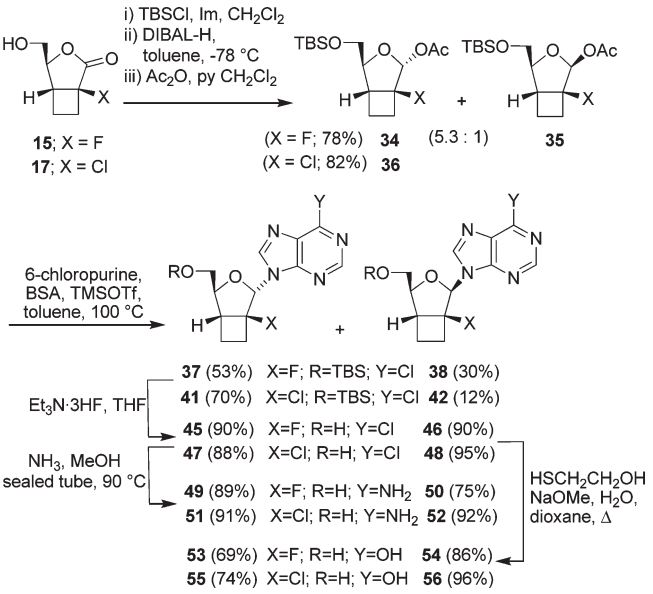

The lower yields of the photochemical reactions with acetylene compared to the corresponding reactions with ethylene can be attributed to secondary photoactivity since the initial cyclobutene photoproducts might undergo excitation leading to further processes, which can also mask the observed anti/syn selectivity of the photocycloaddition.[24] The tricyclic cyclobutene products **25** and **26** might arise from the reaction of the newly formed double bond of the primary [2 + 2] adducts with acetylene. Formation of tricyclic cyclobutene derivatives through two consecutive additions of acetylene had been already reported by Pietra and co-workers[25] in the photochemical reaction of 3-acetoxy-2-cyclopentenone with acetylene.

The structural and stereochemical assignments of the cycloadducts **25** and **26** were established on the basis of 1D and 2D NMR spectroscopy. For instance, for compound **25**, the HMQC experiment showed two allylic methyne groups, C-2 and C-5, while the HMBC spectrum showed correlations between H-1 and C-2, C-3, C-6, and C-10, between H-2 and C-3, C-4, and C-5, between H-4 and C-3 and C-5, and between H-5 and C-6. The relative configuration was determined on the basis of NOESY experiments. Thus, the cross-peak observed between H-3 and H-9 indicates an anti endo stereochemistry.

In summary, the presence of a halogen atom at the α-position of the lactone has a noticeable influence on the chemical yield and stereochemical course on their photochemical reactions with ethylene and acetylene. Considering all the factors implicated in the studied photochemical processes, only the photoreactions involving ethylene are synthetically useful. These reactions furnished the fluoro- and chlorocyclobutanes **15** and **17** in 62% and 58% yield, respectively.

With the major anti cycloadducts **13**, **15**, and **17** in hand, we turned our attention to prepare the target nucleoside analogues. First, we undertook the synthesis of the purine cyclobutene analogues starting from **13** (Scheme 6).

**Scheme 7. Preparation of the Fluoro and Chloro Cyclobutane Purine Analogues**




According to the plan, the protection of the primary hydroxyl group as the *tert*-butyldimethylsilyl ether, followed by partial reduction of the lactone with DIBAL-H in toluene, and treatment of the resulting lactols with acetic anhydride provided the key intermediate **27** in 64% yield for the three steps.

The N-glycosylation reaction of **27** with 6-chloropurine was conducted under modified Vorbrüggen conditions;[26] namely, 6-chloropurine was silylated in situ by reaction with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) in the presence of trimethylsilyltriflate (TMSOTf) in $CH_3CN$ at room temperature. Under these conditions, the condensation reaction proceeded with the formation of the expected *N*9 α- and *β*-anomers **28** and **29** in 86% overall yield and nearly equal amounts. The chromatographic separation of **28** and **29** provided pure samples of the two epimers. Since the α-anomer might also be a valuable candidate for biological assays, alternative conditions to increase the *β*-selectivity of the coupling reaction were not investigated.

The *N*9 attachment site of the purine base in **28** and **29** was deduced from HMBC experiments, which showed correlation between H-1′ and C-4, while the anomeric configuration was elucidated by $^1$H NMR analysis, including NOESY experiments.[27] The isomer displaying a small coupling constant $J_{1',2'}$ (∼0 Hz) was assigned as the *β*-anomer **29**, whereas that with a larger $J_{1',2'}$ (5.4 Hz) was assigned as the α-anomer **28**.

Unmasking of the hydroxyl group of **29** to furnish **31** was accomplished by routine desilylation with tetra-*n*-butylammonium fluoride. Finally, substitutive amination by heating **31** at 90 °C with methanolic ammonia in a sealed vessel for 8 h delivered the targeted cyclobutene nucleoside **33** in 72% yield. An analogous sequence from **28** provided the α-anomer **32** in 72% yield for the two steps.

The synthesis of the fluoro and chloro cyclobutane analogues was carried out in a similar manner (Scheme 7). Thus, the anti cycloadducts **15** and **17** were converted to the corresponding fluoro acetates **34**−**35** and chloro acetate **36** in 78% and 82% overall yield, respectively.


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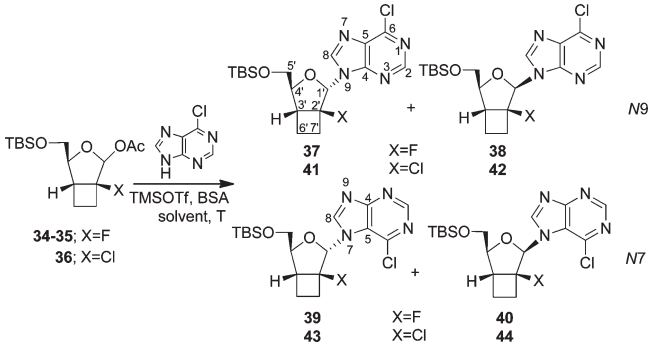
**Table 2. Different Reaction Conditions for the N-Glycosylation Reaction**




| entry | X | solvent | *T* | time | yield (%)[a] | *N*9α:*N*9β:*N*7α:*N*7β (%)[b] | *N*-9:*N*-7 | α:β |
|---|---|---|---|---|---|---|---|---|
| 1 | Cl | acetonitrile | 25 °C | 3.5 h | 87 | 42:4:47:7 | 1:1.2 | 8.1:1 |
| 2 | Cl | acetonitrile | 82 °C | 1 h | 95 | 74:13:8:5 | 6.7:1 | 4.5:1 |
| 3 | Cl | DCE | 25 °C | 27 h | 65 | 31:1:58:10 | 1:2.1 | 8.1:1 |
| 4 | Cl | DCE | 83 °C | 0.5 h | 78 | 70:11:13:6 | 4.3:1 | 4.9:1 |
| 5 | Cl | toluene | 25 °C | 16 h | 38 | 39:5:50:6 | 1:1.3 | 8.1:1 |
| 6 | Cl | toluene | 100 °C | 1 h | 77 | 85:15:-:- | 1:0 | 5.6:1 |
| 7 | F | acetonitrile | 25 °C | 7.5 h | 88 | 28:15:35:22 | 1:1.3 | 3.7:1 |
| 8 | F | DCE | 83 °C | 2.5 h | 77 | 34:20:23:23 | 1.2:1 | 1.3:1 |
| 9 | F | toluene | 100 °C | 1 h | 90 | 59:35:3:3 | 15:1 | 1.6:1 |

[a] Isolated yield after column chromatography. [b] Product ratio was determined by $^1$H NMR.

At first, the N-glycosylation reaction of acetates **34**−**35** and **36** with silylated 6-chloropurine was attempted in acetonitrile at rt, under the same coupling conditions previously used for **27** (Table 2, entries 1 and 7). Surprisingly, in these cases, the condensation reaction resulted in the formation of the expected *N*9 α- and β-isomers (**37** and **38** for X = F and **41** and **42** for X = Cl) along with the corresponding *N*7 coupling products (**39** and **40** for X = F and **43** and **44** for X = Cl). All the isomers were isolated by column chromatography, and their regio- and stereochemistry were assigned by 1D and 2D NMR spectroscopy.

The attachment site of the purine base in the *N*9 isomers **37**−**38** and **41**−**42** was established by HMBC experiments, which showed correlation between H-1′ and the aromatic carbon atoms C-4 and C-8. On the other hand, cross-peaks were observed between H-1′ and C-5 and C-8 for **40**, indicating *N*7 connectivity. However, no cross-peak was observed between H-1′ and C-5 for compounds **39**, **43**, and **44**. In these compounds, the *N*7 connectivity was supported by the higher chemical shift value of the purine C-4 carbon of the *N*7 isomers **39**−**40** and **43**−**44** (∼162 ppm) compared to that of the *N*9 isomers **37**−**38** and **41**−**42** (∼151 ppm), due to the larger steric congestion existing in the latter.[28]

The anomeric configuration of the fluoro derivatives **37**−**40** was established through the analysis of their $^1$H and $^{13}$C NMR spectra. The value of $^2J_{F,C\text{-}1'}$ is a useful tool to determine the configuration of the anomeric position of the 2′-fluoronucleosides.[29] Thus, the $^2J_{F,C\text{-}1'}$ coupling constant values for β-isomers are close to 18 Hz, whereas for the α-isomers they are around 40 Hz. Accordingly, the highest values of the carbon−fluorine coupling constant between C-1′ and F were correlated with the α-anomeric configuration (40.7 Hz for **37** and 38.7 Hz for **39**); meanwhile, the lowest values were correlated with the β-anomeric configuration (17.8 Hz for **38** and 18.1 Hz for **40**). Moreover, both *N*9 and *N*7 β-nucleosides **38** and **40** possess a characteristic long-range coupling between the fluorine atom and the H-8 proton of the purine base that is not observed in their corresponding α-epimers.[30]

The anomeric configuration of the chloro derivatives **41**−**44** was established by NOESY experiments. Thus, the α-anomers **41** and **43** showed clear correlations between H-1′ and H-5′, while the β-anomers **42** and **44** showed correlations between H-1′ and H-4′.

In view of these results and to overcome the undesired *N*7 regioselectivity, alternative coupling reaction conditions were investigated. The effect of the solvent[26] and the temperature[31] on the outcome of the reaction was evaluated (Table 2). Eventually, it was found that by performing the N-glycosylation reaction in toluene at 100 °C the *N*9 isomers were obtained as major products in good yields (entries 6 and 9). Thus, under these conditions, the fluoro acetates **34**−**35** delivered a 15:1 mixture of the α/β *N*9 isomers **37** and **38** and the α/β *N*7 isomers **39** and **40** in 90% overall yield, while the reaction of the chloro acetate **36** proceeded with complete regioselectivity affording a mixture of the α/β *N*9 isomers **41** and **42** in 77% overall yield. With regard to the α/β stereoselectivity of the condensation reaction, the fluoro derivative gave an α:β ratio of 1.6:1, whereas that for the chloro derivative was 5.6:1, suggesting that the chlorine atom acts as an important steric factor in the coupling reaction.

Next, removal of the silyl protecting group of the α-anomers **37** and **41** by treatment with $Et_3N\cdot 3HF$ in THF furnished the alcohols **45** and **47** in 90% and 88% yield, respectively (Scheme 7). Ammonolysis of these intermediates gave the α-adenosine analogues **49** and **51** in 89% and 91% yield, respectively. The same protocol was applied to the β-anomers **38** and **42** to afford the corresponding target β-adenosine analogues **50** and **52** in 68% and 87% yield for the two steps, respectively.

For these compounds, the substitution of the aromatic chlorine atom of the fluoro, **45**−**46**, and the chloro derivatives, **47**−**48**, by a hydroxyl group was also attempted. One of the most


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**Table 3. Some Conformational Parameters of 33, 2, ddA, d4A, and 53**

| compd | $P^a$ (deg) | $\upsilon_{max}{}^b$ (°) | $\chi^c$ (°) | $\gamma^d$ (°) | $d^e$ (Å) |
|---|---|---|---|---|---|
| **33** | 259.8 | 25.7 | −175.5 | −75.6 | 3.4 (4.8) |
| **2** | 228.1 | 22.9 | −157.1 | 173.8 | 3.7 (4.0) |
| ddA | 190.4 | 35.7 | −95.9 | −178.7 | 3.9 (4.5) |
| d4A | 243.5 | 7.5 | −100.2 | 179.8 | 3.9 (4.6) |
| **53** | 247.1 | 27.5 | 163.6 | 56.6 | |

[a] *P*: phase angle of pseudorotation. [b] $\upsilon_{max}$: maximum puckering amplitude. [c] $\chi$: torsion angle O4′−C1′−N9−C4. [d] $\gamma$: torsion angle O5′−C5′−C4′−C3′. [e] *d*: distance between C-5′ and N9 (distance between O5′ and N9).

common methodologies to achieve this transformation is based on the treatment of a 6-chloropurine derivative with 2-mercaptoethanol and sodium methoxide in refluxing aqueous methanol.[32,33] However, all the attempts to prepare the hypoxanthine derivatives using these conditions met with failure. It was eventually found that performing the reaction in refluxing dioxane[34] the targeted fluoro and chloro inosine analogues **53**−**54** and **55**−**56** could be obtained in good yields.

The adenine cyclobutene β-anomer **33** provided adequate crystals for X-ray analysis. Unfortunately, we were unable to grow good-quality crystals for the fluoro and chloro cyclobutane β-anomers, and within this series, only the 2′-fluoro α-hypoxanthine analogue **53** furnished suitable crystals for X-ray analysis.[35] From the crystallographic data of **33** and **53**, we have calculated their pseudorotational parameters, which revealed that the furanose ring of the cyclobutene analogue **33** adopts an O-exo ($_OE$) pucker with a pseudorotational phase angle $P = 259.8°$ and a maximum amplitude of puckering $\upsilon_{max} = 25.7°$, while the furanose ring of **53** presents a C-4′ endo ($^4E$) pucker with a pseudorotation phase angle $P = 247.1°$ and a puckering amplitude of $\nu_{max} = 27.5°$.[36]

The pseudorotational parameters of **33** have been compared to those obtained from the crystallographic data of **2**,[15] d4A,[37] and ddA[38] (Table 3). A close inspection of these parameters showed several significant differences, but all four compounds are settled in the southwest region of the pseudorotational cycle. In terms of puckering, the furanosid ring of **33** ($\upsilon_{max} = 25.7°$) is not as planar as that of d4A ($\upsilon_{max} = 7.5°$), but it is flattened compared to ddA ($\upsilon_{max} = 35.7°$), indicating that the cyclobutene motif limits the conformational flexibility of the sugar moiety. Moreover, the puckering of the furanoside ring of **33** is similar to that of **2** ($\upsilon_{max} = 22.9°$), showing that the pursued additional rigidity induced by the double bond in **33** is not at play. However, puckering amplitude values around 25° are close to a "central conformation" which includes nucleosides with small $\upsilon_{max}$ values of less than 20°. With regard to the glycosidic link, although the purine base in all compounds is anti arranged relative to the sugar moiety, the glycosyl torsion angle $\chi$ values of **33** (−175.5°) and **2** (−157.1°) clearly diverge from those of d4A (−100.2°) and ddA (−95.9°). The main difference between **33** and **2** is the orientation of the hydroxymethyl group (Figure 4). Thus, the value of the torsion angle $\gamma$ of **33** (−75.6°) is strikingly different from those of **2**, d4A, and ddA (~178°). Finally, another remarkable conformational feature of **33** is that the distance between C5′ and N9, an important parameter for the recognition by nucleoside kinases, is comparable to those of **2**, ddA, and d4A.[39]

As a preliminary test, the new synthesized nucleoside analogues were evaluated on MT4 cells for anti-HIV-1 activity against

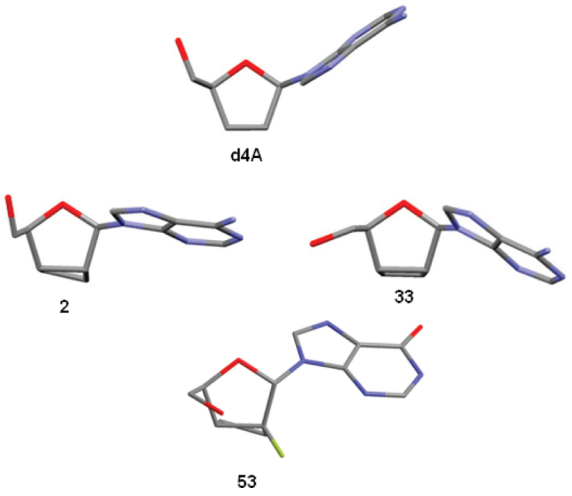


**Figure 4.** X-ray structures of d4A, **2**, **33**, and **53**.

wild-type NL4-3 strain as well as cytotoxicity using d4T and AZT and AMD3100 as the positive control. Unfortunately, only a moderate activity was found for **2** ($EC_{50} = 17.8\ \mu g/mL$ and $CC_{50} > 25\ \mu g/mL$) and **52** ($EC_{50} = 22.92\ \mu g/mL$ and $CC_{50} > 25\ \mu g/mL$), and no activity or toxicity was found for any of the remaining compounds below a concentration of 25 μg/mL.[40] Despite the similar structural motifs of the synthesized compounds and d4A, the weak anti-HIV-1 activity displayed by our compounds may suggest that the ethylene group of the fused cyclobutane makes them poor substrates for the three activating cellular kinases or for the final interaction with the target reverse transcriptase.

## CONCLUSIONS

In summary, purine nucleoside analogues **32**−**33** and **49**−**56** built on a 3-oxabicyclo[3.2.0]heptane scaffold bearing different functionality have been synthesized through glycosylation reactions between 6-chloropurine and suitable sugar precursors containing the 3-oxabicyclo[3.2.0]heptane skeleton **13**, **15**, and **17**. The anti cyclobutene derivative **13** has been stereoselectively prepared by the photoreaction of **4a** with (*Z*)-1,2-dichloroethylene followed by Zn-promoted dechlorination under microwave irradiation, while the halogenated anti cyclobutanes **15** and **17** have been efficiently prepared by the photochemical reaction of lactones **4b** and **4c** with ethylene. The presence of a halogen atom at the α-position of the lactone has a noticeable influence on the outcome of the photochemical process. Structure, conformation, and anti-HIV-1 activity of the new nucleosides have been investigated.

## EXPERIMENTAL SECTION

**General Methods.** Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under a nitrogen atmosphere. Flash column chromatography was performed using silica gel (230−400 mesh). $^1H$ NMR and $^{13}C$ NMR spectra were recorded at 250 and 62.5 MHz or 360 and 90 MHz or 500 and 125 MHz. NMR signals were assigned with the help of DEPT, COSY, HMBC, HMQC, and NOESY experiments. Proton chemical shifts are reported in parts per million (δ) ($CDCl_3$, δ 7.26, $CD_3OD$ δ 3.31, or DMSO-$d_6$, δ 2.50). Carbon chemical shifts are


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reported in parts per million ($\delta$) ($CDCl_3$, $\delta$ 77.2, $CD_3OD$ $\delta$ 49.00, or DMSO-$d_6$, $\delta$ 39.52). NMR signals were assigned with the help of COSY, HSQC, HMBC, and NOESY experiments. Infrared peaks are reported in $cm^{-1}$. Melting points were determined on hot stage and are uncorrected. High-resolution mass spectra (HRMS) were recorded on a mass spectrometer. Optical rotations were measured at 22 ± 2 °C.

Microwave reactions were conducted on a 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.

*Anti HIV-1 Activity and Cytotoxicity.* Anti-HIV activity and citotoxicity were assayed at the Irsicaixa Foundation, University Hospital Germans Trias i Pujol, Badalona, Spain. Anti-HIV activity was tested in a lymphoid cell line MT-4 which was obtained through the MRC AIDS Reagent Program. Briefly, the HIV-1 NL4-3 strain was tittered in MT-4 cells after acute infection and infectivity were measured by evaluating the cytopathic effect induced after 5 day cultures as described.[41] Anti-HIV activity and cytotoxicity measurements in MT-4 cells were based on the viability of cells that had been infected or not infected with HIV-1, all exposed to various concentrations of the test compound. After the MT-4 cells were allowed to proliferate for 5 days, the number of viable cells was quantified by a tetrazolium-based colorimetric method (MTT method) as described.[41a]

*Ethyl (2E)-3-[(4S)-2′,2′-Dimethyl-1′,3′-dioxolan-4′-yl]-2-chloro-2-propenoate (**8**) and Its (2Z)- Isomer (**9**).* To a −78 °C cooled solution of triethyl 2-chloro-2-phosphonacetate (1.02 g, 3.93 mmol) in dry THF (2 mL) was added dropwise BuLi (2.44 mL, 3.91 mmol, 1.6 M) in hexane, and the solution was stirred for 1 h at −78 °C. Then, a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde, **7** (510 mg, 3.91 mmol), in dry THF (2 mL) was added dropwise, and the dark solution was kept at −78 °C for 2 h. The reaction mixture was treated with a saturated aqueous solution of $NH_4Cl$ (2 mL) and was allowed to slowly warm to room temperature. After addition of $CH_2Cl_2$ (5 mL), the aqueous layer was extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic layer was washed with brine (3 × 4 mL), dried over anhydrous $Na_2SO_4$, and evaporated. The resulting dark oil was purified by column chromatography (from hexane to hexane−diethyl ether 30:1) affording the olefins **8** (489 mg, 2.08 mmol, 53% yield) and **9** (80 mg, 0.34 mmol, 9% yield) as colorless oils.

**8**: IR (ATR) 2985, 2937, 1714, 1208, 1058, 1024 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.57 (d, $J_{3,4'}$ = 6.9 Hz, 1H, H-3), 5.29 (ddd, $J_{4',3}$ = 6.9 Hz, $J_{4',5'}$ = 6.8 Hz, $J_{4',5'}$ = 6.3 Hz, 1H, H-4′), 4.32 (dd, $J_{gem}$ = 8.4 Hz, $J_{5',4'}$ = 6.8 Hz, 1H, H-5′), 4.28 (m, 2H, $OCH_2CH_3$), 3.70 (dd, $J_{gem}$ = 8.4 Hz, $J_{5',4'}$ = 6.3 Hz, 1H, H-5′), 1.45 (s, 3H, $CH_3$), 1.38 (s, 3H, $CH_3$), 1.35 (t, $J$ = 7.1 Hz, 3H, $OCH_2CH_3$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 162.0 (C═O, C-1), 144.6 (CH, C-3), 123.7 (C, C-2), 110.0 (C, C-2′), 73.6 (CH, C-4′), 69.3 ($CH_2$, C-5′), 62.5 ($CH_2$, $OCH_2CH_3$), 26.5 ($CH_3$, $C(CH_3)_2$), 25.4 ($CH_3$, $C(CH_3)_2$), 14.0 ($CH_3$, $OCH_2CH_3$). HRMS (ESI+) calcd for $[C_{10}H_{15}ClO_4 + Na]^+$ 257.0551, found 257.0547 (mixture of **8** and **9**).

**9**: IR (ATR) 2985, 2929, 1726, 1240, 1060, 1030 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 7.05 (d, $J_{3,4'}$ = 6.9 Hz, 1H, H-3), 4.97 (ddd, $J_{4',3}$ = 6.9 Hz, $J_{4',5'}$ = 6.8 Hz, $J_{4',5'}$ = 6.8 Hz, 1H, H-4), 4.24 (m, 3H, H-5′, $OCH_2CH_3$), 3.66 (dd, $J_{gem}$ = 8.4 Hz, $J_{5',4'}$ = 6.8 Hz, 1H, H-5′), 1.40 (s, 3H, $CH_3$), 1.35 (s, 3H, $CH_3$), 1.29 (t, $J$ = 7.1 Hz, 3H, $OCH_2CH_3$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 161.5 (C═O, C-1), 140.0 (CH, C-3), 125.7 (C, C-2), 110.1 (C, C-2′), 73.3 (CH, C-4′), 68.1 ($CH_2$, C-5′), 62.5 ($CH_2$, $OCH_2CH_3$), 26.3 ($CH_3$, $C(CH_3)_2$), 25.4 ($CH_3$, $C(CH_3)_2$), 14.0 ($CH_3$, $OCH_2CH_3$).

*(5S)-3-Chloro-5-hydroxymethyl-2(5H)-furanone (**4c**).* To a solution of **8** (300 mg, 1.28 mmol) in EtOH (10 mL) at 0 °C was added concentrated HCl (0.4 mL, 5.12 mmol). The mixture was allowed to warm to room temperature and stirred for 4 h. Then, the solvent was removed and the residue coevaporated with toluene (2 × 2 mL). The resulting crude was purified by column chromatography (EtOAc) yielding **4c** (180 mg, 1.21 mmol, 95% yield) as a colorless oil: $[\alpha]_D$ −54.0 (*c* 1.0, $CHCl_3$); IR (ATR) 3409, 3097, 1752, 1029 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 7.35 (d, $J_{4,5}$ = 1.9 Hz, 1H, H-4), 5.12 (ddd, $J_{5,6}$ = 4.8 Hz, $J_{5,6}$ = 3.8 Hz, $J_{5,4}$ = 1.9 Hz, 1H, H-5), 4.00 (dd, $J_{gem}$ = 12.3 Hz, $J_{6,5}$ = 3.8 Hz, 1H, H-6), 3.83 (dd, $J_{gem}$ = 12.3 Hz, $J_{6,5}$ = 4.8 Hz, 1H, H-6), 2.37 (br s, 1H, OH); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 167.7 (C═O, C-2), 145.0 (CH, C-4), 126.1 (C, C-3), 81.5 (CH, C-4), 62.3 ($CH_2$, C-6). HRMS (ESI+) calcd for $[C_5H_5ClO_3 + Na]^+$ 170.9819, found 170.9825.

**General Procedure for the Photochemical Reactions.** Irradiations were performed in a small conventional photochemical reactor (two-necked vessel fitted with a Pyrex or quartz immersion type cooling jacket) using a high-pressure 125 W mercury lamp. Methanol at −15 °C was used for refrigeration of the immersion well jacket. The vessel was externally cooled at −20 °C with a dry ice−$CCl_4$ bath or at −40 °C with a dry ice−acetonitrile bath. Ethylene or acetylene (acetone free) gas was bubbled through the solution for 15 min. Once the lamp was turned on, a slow flow of gas was maintained throughout the irradiation. *Caution: acetylene is hazardous and subject to strict safety regulations.* The photochemical reactions with (*Z*)-1,2-dichloroethylene were initially degassed by passage of oxygen-free argon through the solution for 10 min and then irradiated under an atmosphere of argon. The progress of the reactions was monitored by GC or $^1H$ NMR analysis of aliquot samples.

*(1R,4S,5S)- and (1S,4S,5R)-4-Hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (**13** and **14**). Method A.* A solution of (5*S*)-4-hydroxymethyl-2(5*H*)-furanone, **4a** (357 mg, 3.1 mmol), and (*Z*)-1,2-dichloroethylene (1.18 mL, 15.6 mmol) in acetonitrile (280 mL) was irradiated through a Quartz filter for 5 h at −20 °C. Evaporation of the solvent and column chromatography (from hexane−EtOAc 10:1 to EtOAc) afforded a diastereomeric mixture of the dichlorocyclobutane derivatives.The resulting crude was dissolved in (80%) aqueous EtOH (4 mL), and activated Zn dust (4.0 g, 61.2 mmol) was added. The mixture was irradiated under pressure in a focused microwave reactor at 100 °C for 15 min. After cooling, the 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 1:2) to afford a mixture of the two diastereomers **13** and **14** (328 mg, 2.34 mmol, 75% yield) in a ratio (90:10). A further column chromatography (from hexane−EtOAc 2:1 to hexane−EtOAc 1:1) allowed us to isolate pure **13** (262 mg, 1.87 mmol, 65% yield) as a colorless oil.

*Method B.* A solution of 2(5*H*)-furanone **4a** (112 mg, 0.98 mmol) in freshly distilled acetone (65 mL) saturated with acetylene was irradiated through a Pyrex filter for 5.5 h at −20 °C. Evaporation of the solvent and column chromatography (hexane−EtAcO 1:1) afforded a 65:35 mixture of the cycloadducts **13** and **14** (60 mg, 0.43 mmol, 44% yield) and some unreacted **4a** (19 mg, 0.17 mmol, 17%). Repeated column chromatography (from hexane−EtAcO 3:1 to hexane−EtAcO 1:1) allowed us to isolate **13** and an enriched fraction of **14**.

**13**: IR (ATR) 3422, 3056, 2939, 2874, 1737, 1171 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.34 (d, $J_{6,7}$ = 2.6 Hz, 1H, H-6), 6.26 (d, $J_{7,6}$ = 2.6 Hz, 1H, H-7), 4.45 (ddd, $J_{4,8}$ = 3.6 Hz, $J_{4,8}$ = 3.6 Hz, $J_{4,5}$ = 1.7 Hz, 1H, H-4), 3.86 (dd, $J_{gem}$ = 12.2 Hz, $J_{8,4}$ = 3.6 Hz, 1H, H-8), 3.67 (d, $J_{1,5}$ = 3.5 Hz, 1H, H-1), 3.62 (dd, $J_{gem}$ = 12.2 Hz, $J_{8,4}$ = 3.6 Hz, 1H, H-8), 3.48 (dd, $J_{5,1}$ = 3.5 Hz, $J_{5,4}$ = 1.7 Hz, 1H, H-5), 2.99 (br s, 1H, OH); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.1 (C═O, C-2), 141.2 (CH, C-6), 138.6 (CH, C-7), 79.5 (CH, C-4), 64.4 ($CH_2$, C-8), 47.9 (CH, C-1), 44.1 (CH, C-5). HRMS (ESI+) calcd for $[C_7H_8O_3+H]^+$ 141.0552, found 141.0554.

**14**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 6.44 (t, $J$ = 2.6 Hz, 1H, H-6), 6.39 (t, $J$ = 2.2 Hz, 1H, H-7), 4.54 (ddd, $J_{4,8}$ = 4.3 Hz, $J_{4,8}$ = 4.3 Hz, $J_{4,5}$ = 4.3 Hz, 1H, H-4), 3.95−3.45 (m, 4H, H-1, H-5, H-8), 1.94 (br s, 1H, OH); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 176.1 (C═O, C-2), 139.3 (CH, C-6), 138.7 (CH, C-7), 78.6 (CH, C-4), 62.6 ($CH_2$, C-8), 43.5 (CH, C-1), 40.1 (CH, C-5).

*(1S,4S,5R)- and (1R,4S,5S)-1-Fluoro-4-hydroxymethyl-3-oxabicyclo-[3.2.0]heptan-2-one (**15** and **16**).* A solution of the 3-fluoro-2(5*H*)-furanone **4b** (135 mg, 1.02 mmol) in freshly distilled acetone (65 mL) saturated with ethylene was irradiated through a Pyrex filter for 3.5 h at −20 °C. Evaporation of the solvent and column chromatography (hexane−EtOAc 3:1) afforded a 81:19 mixture of the cycloadducts **15** and **16** (131 mg, 0.81 mmol, 80% yield). Repeated column chromatography (from hexane−EtOAc 5:1 to hexane−EtOAc 3:1) allowed us to isolate pure **15** (101 mg, 0.63 mmol, 62% yield) as a white solid and an enriched fraction of **16**.

**15**: Mp 99−102 °C (from EtOAc); $[\alpha]_D$ −36.0 (*c* 1.3, $CHCl_3$); IR (ATR) 3331, 2959, 1780, 1766, 1037 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.45 (ddd, $J_{4,8}$ = 4.4 Hz, $J_{4,F}$ = 3.9 Hz, $J_{4,8}$ = 3.4 Hz, 1H, H-4), 3.83 (dd, $J_{gem}$ = 12.3 Hz, $J_{8,4}$ = 3.4 Hz, 1H, H-8), 3.68 (dd, $J_{gem}$ = 12.3 Hz, $J_{8,4}$ = 4.4 Hz, 1H, H-8), 3.20 (ddd, $J$ = 17.2 Hz, $J$ = 10.6 Hz, $J$ = 6.9 Hz, 1H, H-5), 2.61 (m, 1H, H-7exo), 2.50 (m, 1H, H-7endo), 2.36 (m, 1H, H-6exo), 2.22 (br s, 1H, OH), 1.54 (m, 1H, H-6); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 173.9 (d, $^2J_{C-F}$ = 25.9 Hz, C═O), 90.1 (d, $^1J_{C-F}$ = 243.4 Hz, C, C-1), 84.1 (s, CH, C-4), 63.6 (s, $CH_2$, C-8), 41.9 (d, $^2J_{C-F}$ = 17.7 Hz, CH, C-5), 28.8 (d, $^2J_{C-F}$ = 23.8 Hz, CH, C-7), 15.4 (d, $^3J_{C-F}$ = 16.1 Hz, CH, C-6); $^{19}$F NMR (235 MHz, $CDCl_3$) $\delta$ −150.6 to −150.8 (m). Anal. Calcd for ($C_7H_9FO_3$): C, 52.50; H, 5.66. Found: C, 52.62; H, 5.72.

**16**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 4.37 (ddd, $J_{4,8}$ = 7.3 Hz, $J_{4,5}$ = 4.9 Hz, $J_{4,8}$ = 4.6 Hz, 1H, H-4), 3.91 (dd, $J_{gem}$ = 12.2 Hz, $J_{8,4}$ = 7.3 Hz, 1H, H-8), 3.75 (dd, $J_{gem}$ = 12.2 Hz, $J_{8,4}$ = 4.6 Hz, 1H, H-8), 3.35 (m, 1H, H-5), 2.57 (m, 1H, H-7), 2.51 (m, 1H, H-7), 2.10 (m, 1H, H-6), 1.75 (br s, 1H, OH), 1.65 (m, 1H, H-6); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 173.0 (d, $^2J_{C-F}$ = 26.1 Hz, C═O), 90.5 (d, $^1J_{C-F}$ = 243.8 Hz, C, C-1), 80.7 (s, CH, C-4), 61.6 (s, $CH_2$, C-8), 42.6 (d, $^2J_{C-F}$ = 18.8 Hz, CH, C-5), 28.3 (d, $^2J_{C-F}$ = 21.8 Hz, CH, C-7), 9,8 (d, $^3J_{C-F}$ = 16.3 Hz, CH, C-6); $^{19}$F NMR (235 MHz, $CDCl_3$) $\delta$ −150.8 to −151.0 (m).

*(1S,4S,5R)-1-Chloro-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (**17**) and (6R,7R)- and (6R,7S)-7-Chloro-6-hydroxymethyl-5-oxaspiro[2.4]heptan-4-one (**23** and **24**).* A solution of the 3-chloro-2(5*H*)-furanone **4c** (148 mg, 1.00 mmol) in freshly distilled acetone (65 mL) saturated with ethylene was irradiated through a Pyrex filter for 4.5 h at −20 °C. Evaporation of the solvent and column chromatography (hexane−EtAcO 3:1) delivered a 72:11:17 mixture of **17**, **23**, and **24** (148 mg, 0.83 mmol, 85% yield). Repeated column chromatography (from hexane−EtAcO 5:1 to hexane−EtAcO 3:1) allowed us to isolate **17** (102 mg, 0.57 mmol, 58% yield), **23** (14 mg, 0.08 mmol, 85% yield), and **24** (22 mg, 0.12 mmol, 13% yield) as colorless oils.

**17**: $[\alpha]_D$ +12.7 (*c* 1.1, $CHCl_3$); IR (ATR) 3400, 2950, 2872, 1766, 1223 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 4.46 (dd, $J_{4,8}$ = 4.9 Hz, $J_{4,8}$ = 4.7 Hz, 1H, H-4), 3.76 (m, 2H, H-8), 3.22 (ddd, $J_{5,6}$ = 7.0 Hz, $J_{5,6}$ = 1.7 Hz, $J_{5,4}$ = 0.5 Hz, 1H, H-5), 2.67 (m, 1H, H-7), 2.60 (m, 1H, H-7), 2.51 (m, 1H, H-6exo), 2.49 (br s, 1H, OH), 1.88 (m, 1H, H-6endo); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 175.5 (C═O, C-2), 84.4 (CH, C-4), 63.1 ($CH_2$, C-8), 59.5 (C, C-1), 45.7 (CH, C-5), 33.4 ($CH_2$, C-7), 20.2 ($CH_2$, C-6). HRMS (ESI+) calcd for $[C_7H_9ClO_3 + Na]^+$ 199.0132, found 199.0129.

**23**: Mp 39−41 °C (from EtOAc); $[\alpha]_D$ +172.2 (*c* 1.8, $CHCl_3$); IR (ATR) 3432, 2970, 1742, 1149, 1044 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.82 (ddd, $J_{6,8}$ = 6,7 Hz, $J_{6,8}$ = 5.0 Hz, $J_{6,7}$ = 5.0 Hz, 1H, H-6), 4.50 (d, $J_{7,6}$ = 5.0 Hz, 1H, H-7), 4.14 (dd, $J_{gem}$ = 12.3 Hz, $J_{8,6}$ = 6.7 Hz, 1H, H-8), 4.00 (dd, $J_{gem}$ = 12.3 Hz, $J_{8,6}$ = 5.0 Hz, 1H, H-8), 3.18 (br s, 1H, OH), 1.59−1.30 (m, 4H, H-1, H-2); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 176.2 (C═O, C-4), 80.0 (CH, C-6), 62.8 (CH, C-7), 62.2 ($CH_2$, C-8), 28.6 (C, C-3), 19.0/13.5 ($2CH_2$, C-1, C-2). HRMS (ESI+) calcd for $[C_7H_9ClO_3 + Na]^+$ 199.0132, found 199.0132.

**24**: $[\alpha]_D$ −69.7 (*c* 2.54, $CHCl_3$); IR (ATR) 3423, 2934, 1755, 1112, 1055 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 4.73 (ddd, $J_{6,8}$ = 3.5 Hz, $J_{6,8}$ = 3.3 Hz, $J_{6,7}$ = 3.3 Hz, 1H, H-6), 4.49 (d, $J_{7,6}$ = 3.3 Hz, 1H, H-7), 3.95 (dd, $J_{gem}$ = 12.7 Hz, $J_{8,6}$ = 3.3 Hz, 1H, H-8), 3.79 (dd, $J_{gem}$ = 12.7 Hz, $J_{8,6}$ = 3.5 Hz, 1H, H-8), 3.32 (br s, 1H, OH), 1.48−1.27 (m, 4H, H-1, H-2); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 177.6 (C═O, C-4), 86.4 (CH, C-6), 61.6 ($CH_2$, C-8), 59.8 (CH, C-7), 28.1 (C, C-3), 19.2/15.6 ($2CH_2$, C-1, C-2). HRMS (ESI+) calcd for $[C_7H_9ClO_3 + Na]^+$ 199.0132, found 199.0134.

*(1S,4S,5R)- and (1R,4S,5S)-1-Fluoro-4-hydroxymethyl-3-oxabicyclo-[3.2.0]hept-6-en-2-one (**19** and **20**) and (1R,2S,5R,6S,9S)-6-Fluoro-9-hydroxymethyl-8-oxatricyclo[4.3.0.0$^{2,5}$]non-3-en-7-one (**25**).* A solution of lactone **4b** (130 mg, 0.98 mmol) in freshly distilled acetone (65 mL) saturated with acetylene was irradiated through a Pyrex filter for 5.5 h at −20 °C. Evaporation of the solvent and column chromatography (from hexane−EtOAc 6:1 to hexane−EtOAc 4:1) afforded the following fractions: (i) a 95:5 mixture of the cyclobutene derivatives **19** and **20** (44 mg, 0.27 mmol, 28% yield) as a colorless oil; (ii) the tricyclic derivative **25** (27 mg, 0.15 mmol, 15%) as a colorless oil; and (iii) some unreacted **4b** (45 mg, 0.34 mmol, 35%).

**19**: IR (ATR) 3404, 2937, 2878, 1761, 1075 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 6.57 (ddd, $J_{6,F}$ = 11.4 Hz, $J_{6,7}$ = 2.8 Hz, $J_{6,5}$ = 0.6 Hz, 1H, H-6), 6.43 (ddd, $J_{7,6}$ = 2.7 Hz, $J_{7,F}$ = 1.3 Hz, $J_{7,5}$ = 0.6 Hz, 1H, H-7), 4.38 (dddd, $J_{4,F}$ = 4.5 Hz, $J_{4,8}$ = 3.2 Hz, $J_{4,8}$ = 2.9 Hz, $J_{4,5}$ = 1.5 Hz, 1H, H-4), 3.94 (dd, $J_{gem}$ = 12.2 Hz, $J_{8,4}$ = 2.9 Hz, 1H, H-8), 3.71 (dd, $J_{gem}$ = 12.2 Hz, $J_{8,4}$ = 3.2 Hz, 1H, H-8), 3.59 (dddd, $J_{5,F}$ = 2.6 Hz, $J_{5,4}$ = 1.5 Hz, $J_{5,6}$ = 0.6 Hz, $J_{5,7}$ = 0.6 Hz, 1H, H-5); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 171.0 (d, $^2J_{C-F}$ = 28.9 Hz, C═O, C-2), 141.3 (d, $^3J_{C-F}$ = 15.6 Hz, CH, C-6), 138.6 (d, $^2J_{C-F}$ = 26.2 Hz, CH, C-7), 91.6 (d, $^1J_{C-F}$ = 248.2 Hz, C, C-1), 78.3 (s, CH, C-4), 63.5 (s, $CH_2$, C-8), 49.6 (d, $^2J_{C-F}$ = 16.4 Hz, CH, C-5); $^{19}$F NMR (235 MHz, $CDCl_3$) $\delta$ −165.6 to −165.9 (m). HRMS (ESI+) calcd for $[C_7H_7FO_3 + Na]^+$ 181.0199, found 181.0193 (mixture **19** and **20**).

**20**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 6.71 (ddd, $J_{6,F}$ = 7.9 Hz, $J_{6,7}$ = 2.9 Hz, $J_{6,5}$ = 0.7 Hz, 1H, H-6), 6.23 (br d, $J_{7,6}$ = 2.9 Hz, 1H, H-7), 4.95 (m, 1H, H-4), 3.98 (dd, $J_{gem}$ = 12.3 Hz, $J_{8,4}$ = 2.8 Hz, 1H, H-8), 3.79 (dd, $J_{gem}$ = 12.3 Hz, $J_{8,4}$ = 4.9 Hz, 1H, H-8), 3.60 (m, 1H, H-5).

**25**: $[\alpha]_D$ +28.9 (*c* 0.44, $CHCl_3$); IR (ATR) 3399, 2940, 1762, 1225, 1063 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 6.45 (m, 1H, H-3), 6.19 (ddd, $J$ = 2.6 Hz, $J_{4,2}$ = 2.1 Hz, $J$ = 0.7 Hz, 1H, H-4), 4.34 (dddd, $J_{9,F}$ = 6.4 Hz, $J_{9,10}$ = 4.3 Hz, $J_{9,10}$ = 3.2 Hz, $J_{9,1}$ = 1.9 Hz, 1H, H-9), 3.84 (dd, $J_{gem}$ = 12.3 Hz, $J_{10,9}$ = 3.2 Hz, 1H, H-10), 3.78 (m, 1H, H-5), 3.68 (dd, $J_{gem}$ = 12.3 Hz, $J_{10,9}$ = 4.3 Hz, 1H, H-10), 3.56 (dddd, $J_{2,1}$ = 8.0 Hz, $J$ = 5.9 Hz, $J$ = 3.4 Hz, $J_{2,4}$ = 2.1 Hz, 1H, H-2), 3.09 (dddd, $J_{1,F}$ = 16.9 Hz, $J_{1,2}$ = 8.0 Hz, $J_{1,9}$ = 1.9 Hz, $J_{1,3}$ = 1.0 Hz, 1H, H-5), 2.19 (br s, 1H, OH); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 171.8 (d, $^2J_{C-F}$ = 25.2 Hz, C═O, C-7), 140.7 (d, $^4J_{C-F}$ = 3.3 Hz, CH, C-3), 137.8 (d, $^3J_{C-F}$ = 4.2 Hz, CH, C-4), 95.9 (d, $^1J_{C-F}$ = 238.9 Hz, C, C-6), 82.3 (d, $^3J_{C-F}$ = 3.9 Hz, CH, C-9), 64.0 (s, $CH_2$, C-10), 49.9 (d, $^2J_{C-F}$ = 49.9 Hz, CH, C-5), 38.4 (d, $^3J_{C-F}$ = 4.6 Hz, CH, C-2), 37.9 (d, $^2J_{C-F}$ =16.9 Hz, $CH_2$, C-1); $^{19}$F NMR (235 MHz, $CDCl_3$) $\delta$ −168.0 to −168.2 (m). HRMS (ESI+) calcd for $[C_9H_9FO_3 + Na]^+$ 207.0428, found 207.0430.

*(1S,4S,5R)-1-Chloro-4-hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (**21**) and (1R,2S,5R,6S,9S)-6-Chloro-9-hydroxymethyl-8-oxatricyclo[4.3.0.0$^{2,5}$]non-3-en-7-one (**26**).* A solution of lactone **4c** (149 mg, 1.00 mmol) in freshly distilled acetone (65 mL) saturated with acetylene was irradiated through a Pyrex filter for 4.5 h at −20 °C. Evaporation of the solvent and column chromatography (hexane−EtAcO 3:1) afforded the cycloadduct **21** (29 mg, 0.17 mmol, 17% yield) as a colorless oil, the tricyclic derivative **26** (12 mg, 0.06 mmol, 6% yield) as a colorless oil, and some unreacted **4c** (36 mg, 0.24 mmol, 24%).

**21**: $[\alpha]_D$ −71.1 (*c* 2.54, $CHCl_3$); IR (ATR) 3405, 2933, 1755, 957 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 6.50 (dd, $J_{6,7}$ = 2.6 Hz,

$J_{6,5}$ = 0.6 Hz, 1H, H-6), 6.37 (d, $J_{7,6}$ = 2.6 Hz, 1H, H-7), 4.44 (ddd, $J_{4,8}$ = 3.5 Hz, $J_{4,8}$ = 3.0 Hz, $J_{4,5}$ = 1.5 Hz, 1H, H-4), 3.93 (dd, $J_{gem}$ = 12.0 Hz, $J_{8,4}$ = 3.0 Hz, 1H, H-8), 3.72 (dd, $J_{gem}$ = 12.0 Hz, $J_{8,4}$ = 3.5 Hz, 1H, H-8), 3.60 (dd, $J_{5,4}$ = 1.0 Hz, $J_{5,6}$ = 0.6 Hz, 1H, H-5), 2.08 (br s, 1H, OH); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 171.5 (C═O, C-2), 140.5 (CH, C-7), 139.7 (CH, C-6), 78.1 (CH, C-4), 64.0 (C, C-1), 63.7 ($CH_2$, C-8), 53.5 (CH, C-5). HRMS (ESI+) calcd for $[C_7H_7ClO_3+Na]^+$ 196.9976, found 196.9972.

**26**: IR (ATR) 3395, 2942, 2860, 1765, 1080 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.49 (dd, $J_{3,5}$ = 2.6 Hz, $J_{3,4}$ = 2.4 Hz, 1H, H-3), 6.35 (dd, $J_{4,3}$ = 2.4 Hz, $J_{4,2}$ = 2.1 Hz, 1H, H-4), 4.39 (ddd, $J_{9,10}$ = 4.6 Hz, $J_{9,10}$ = 3.4 Hz, $J_{9,1}$ = 1.8 Hz, 1H, H-9), 3.81 (dd, $J_{gem}$ = 12.3 Hz, $J_{10,9}$ = 3.4 Hz, 1H, H-10), 3.75 (dd, $J_{5,2}$ = 2.8 Hz, $J_{5,3}$ = 2.6 Hz, 1H, H-5), 3.68 (dd, $J_{gem}$ = 12.3 Hz, $J_{10,9}$ = 4.6 Hz, 1H, H-10), 3.65 (ddd, $J_{2,1}$ = 7.9 Hz, $J_{2,5}$ = 2.7 Hz, $J_{2,4}$ = 2.1 Hz, 1H, H-2), 3.15 (dd, $J_{1,2}$ = 7.9 Hz, $J_{1,9}$ = 1.8 Hz, 1H, H-5), 1.90 (br s, 1H, OH); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.3 (C═O, C-7), 140.2/139.7 (2CH, C-3, C-4), 77.2 (CH, C-9), 64.0 ($CH_2$, C-10), 63.1 (C, C-6), 53.4 (CH, C-1), 43.6 (CH, C-5), 40.1 (CH, C-2). HRMS (ESI+) calcd for $[C_9H_9ClO_3 + Na]^+$ 223.0132, found 223.0135.

*(1R,4S,5S)-4-tert-Butyldimethylsilyloximethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (**13a**).* To an ice-cooled solution of **13** (417 mg, 2.98 mmol) in $CH_2Cl_2$ (20 mL) were added imidazole (283 mg, 4.16 mmol) and *tert*-butyl dimethylsilyl chloride (584 mg, 3.87 mmol). The mixture was allowed to stir 3 h at room temperature and then was diluted with $CH_2Cl_2$ (10 mL) and washed with water (10 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered, and concentrated to dryness. The reaction crude was purified by column chromatography (hexane−EtOAc, 10:1) to give **13a** (585 mg, 2.30 mmol, 77% yield) as a white solid: mp 49−50 °C (from EtOAc−pentane); $[\alpha]_D$ −221.9 (*c* 0.55, $CHCl_3$); MS (ESI+) 255 ($[M + H]^+$, 28), 277 ($[M + Na]^+$, 50); IR (ATR) 2957, 2926, 2856, 1750, 1250, 1171, 1111 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 6.32 (ddd, $J_{6,7}$ = 2.7 Hz, $J_{6,5}$ = 0.7 Hz, $J_{6,1}$ = 0.7 Hz, 1H, H-6), 6.26 (dd, $J_{7,6}$ = 2.7 Hz, $J_{7,1}$ = 0.8 Hz, 1H, H-7), 4.39 (dddd, $J_{4,8}$ = 2.9 Hz, $J_{4,8}$ = 2.2 Hz, $J_{4,5}$ = 1.3 Hz, $J_{4,1}$ = 0.6 Hz, 1H, H-4), 3.83 (dd, $J_{gem}$ = 10.9 Hz, $J_{4,8}$ = 2.9 Hz, 1H, H-8), 3.63 (dd, $J_{gem}$ = 10.9 Hz, $J_{4,8}$ = 2.2 Hz, 1H, H-8), 3.59 (dddd, $J_{1,5}$ = 3.5 Hz, $J_{1,6}$ = 0.7 Hz, $J_{1,4}$ = 0.7 Hz, $J_{1,7}$ = 0.7 Hz, 1H, H-1), 3.48 (ddd, $J_{5,1}$ = 3.5 Hz, $J_{5,4}$ = 1.3 Hz, $J_{5,6}$ = 0.6 Hz, 1H, H-5), 0.86 (s, 9H, C($CH_3$)$_3$), 0.05 (s, 3H, $CH_3$Si), 0.04 (s, 3H, $CH_3$Si); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 175.5 (C═O), 140.9 (CH, C-6), 138.9 (CH, C-7), 78.6 (CH, C-4), 65.0 ($CH_2$, C-8), 48.2 (CH, C-1), 44.6 (CH, C-5), 25.7 ($CH_3$, C($CH_3$)$_3$), 18.0 (C, *C*($CH_3$)$_3$), −5.7 ($CH_3$Si), −5.7 ($CH_3$Si). Anal. Calcd for ($C_{13}H_{22}O_3Si$): C, 61.38; H, 8.72. Found: C, 61.47; H, 8.74.

*(1R,2RS,4S,5S)-2-Acetyloxy-4-tert-butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]hept-6-ene (**27**).* To a solution of **13a** (398 mg, 1.56 mmol) in dry toluene (45 mL) at −78 °C was added dropwise a 1.0 M solution of DIBAL-H in toluene (7.8 mL, 7.8 mmol) over a period of 30 min under nitrogen atmosphere. After 2 h of stirring at −78 °C, the reaction mixture was quenched by the slow addition of methanol (2 mL) and allowed to warm to room temperature. EtOAc (4 mL) and a saturated $NaHCO_3$ solution (1 mL) were added. After 20 min of vigorous stirring, anhydrous $Na_2SO_4$ (6.6 g) was added. The suspension was stirred vigorously overnight, filtered through Celite, and concentrated to dryness, affording a crude reaction which was used in the next reaction without further purification. To an ice-cooled solution of this crude in $CH_2Cl_2$ (15 mL), pyridine (2.5 mL) and acetic anhydride (2.2 mL) were successively added dropwise. The reaction mixture was stirred at room temperature overnight. Then, the reaction was washed with HCl 5% (2 × 10 mL), saturated $NaHCO_3$ solution (3 × 10 mL), and brine (10 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. The crude residue was purified by column chromatography (hexane−EtOAc, 10:1) to give **27** (385 mg, 1.29 mmol, 83% yield for the 2 steps) as a colorless oil: $[\alpha]_D$ −94.2 (*c* 0.55, $CHCl_3$); MS (ESI+) 321 ($[M + Na]^+$, 100); IR (ATR) 2958, 2930, 2856, 1740, 1226 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 6.13 (m, 3H, H-6, H-7, H-2), 4.06 (dddd, $J_{4,8}$ = 9.0 Hz, $J_{4,8}$ = 5.5 Hz, $J_{4,5}$ = 0.9 Hz, $J_{4,1}$ = 0.5 Hz, 1H, H-4), 3.64 (dd, $J_{gem}$ = 9.9 Hz, $J_{8,4}$ = 5.5 Hz, 1H, H-8), 3.49 (dd, $J_{gem}$ = 9.9 Hz, $J_{8,4}$ = 9.0 Hz, 1H, H-8), 3.48 (m, 1H, H-1), 3.41 (m, 1H, H-5), 2.02 (s, 3H, $CH_3$CO), 0.90 (s, 9H, C($CH_3$)$_3$), 0.07 (s, 6H, 2 × $CH_3$Si); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 170.0 (C═O), 140.5 (CH, C-6), 136.9 (CH, C-7), 97.7 (CH, C-2), 80.8 (CH, C-4), 64.6 ($CH_2$, C-8), 53.4 (CH, C-1), 48.6 (CH, C-5), 25.8 ($CH_3$, C($CH_3$)$_3$), 21.5 ($CH_3$, $CH_3$CO), 18.3 (C, *C*($CH_3$)$_3$), −5.3 ($CH_3$, $CH_3$Si), −5.4 ($CH_3$, $CH_3$Si). Anal. Calcd for ($C_{15}H_{26}O_4Si$): C, 60.37; H, 8.78. Found: C, 60.25; H, 8.53.

*(1′R,2′S,4′S,5′S)- and (1′R,2′R,4′S,5′S)-6-Chloro-9-(4-tert-butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-yl)-9H-purine (**28** and **29**).* BSA (1.06 mL, 4.13 mmol) was added to a suspension of 6-chloropurine (319 mg, 2.06 mmol) in dry acetonitrile (15 mL) under an argon atmosphere. The reaction was allowed to stir for 20 min and cooled to 0 °C. Then, a solution of **27** (411 mg, 1.38 mmol) in dry acetonitrile (4 mL) and TMSOTf (346 $\mu$L, 1.79 mmol) was successively added, and the reaction mixture was stirred at room temperature for 2 h. $CH_2Cl_2$ (25 mL) was added, and the reaction was quenched with an aqueous saturated solution of $NaHCO_3$ (10 mL). The two layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and evaporated to dryness. The crude residue was purified by column chromatography (hexane−EtOAc, 6:1) to give the α-anomer **28** (220 mg, 0.56 mmol, 41% yield) as a white solid and the $\beta$-anomer **29** (243 mg, 0.62 mmol, 45% yield) as a white solid.

**28**: Mp 125−126 °C (from EtOAc−pentane); $[\alpha]_D$ −95.0 (*c* 0.80, $CHCl_3$); IR (ATR) 3107, 3049, 2952, 2930, 2852, 1591, 1559, 1335, 1214 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 8.70 (s, 1H, H-2), 8.42 (s, 1H, H-8), 6.49 (d, $J_{2',1'}$ = 5.4 Hz, 1H, H-2′), 6.37 (d, $J_{6',7'}$ = 2.8 Hz, 1H, H-6′), 5.64 (d, $J_{7',6'}$ = 2.8 Hz, 1H, H-7′), 4.17 (m, 1H, H-4′), 3.90 (m, 1H, H-1′), 3.84 (dd, $J_{gem}$ = 10.8 Hz, $J_{8',4'}$ = 3.5 Hz, 1H, H-8′), 3.67 (dd, $J_{gem}$ = 10.8 Hz, $J_{8',4'}$ = 3.0 Hz, 1H, H-8′), 3.58 (m, *J* = 3.5 Hz, 1H, H-5′), 0.94 (s, 9H, C($CH_3$)$_3$), 0.10 (s, 3H, $CH_3$Si), 0.09 (s, 3H, $CH_3$Si); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 151.9 (CH, C-2), 150.9/150.6 (C, C-4/C-6), 143.6 (CH, C-8), 142.1 (CH, C-6′), 134.6 (CH, C-7′), 131.6 (C, C-5), 83.9 (CH, C-2′), 77.4 (CH, C-4′), 66.2 ($CH_2$, C-8′), 51.3 (CH, C-1′), 49.3 (CH, C-5′), 25.8 ($CH_3$, C($CH_3$)$_3$), 18.1 (C, *C*($CH_3$)$_3$), −5.5 ($CH_3$, $CH_3$Si), −5.6 ($CH_3$, $CH_3$Si). Anal. Calcd for ($C_{18}H_{25}ClN_4O_2Si$): C, 55.02; H, 6.41; N, 14.26. Found: C, 55.25; H, 6.47; N, 14.07.

**29**: Mp 79−80 °C (from EtOAc−pentane); $[\alpha]_D$ −18.7 (*c* 0.75, $CHCl_3$); IR (ATR) 3046, 2854, 2926, 2853, 1590, 1552, 1250. 1073 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 8.74 (s, 1H, H-2), 8.48 (s, 1H, H-8), 6.37 (dt, $J_{7',6'}$ = 2.8 Hz, $J_{7',1'}$ = 0.7 Hz, $J_{7',5'}$ = 0.7 Hz, 1H, H-7′), 6.32 (m, $J_{6',7'}$ = 2.8 Hz, 1H, H-6′), 6.19 (s, 1H, H-2′), 4.44 (m, $J_{1',5'}$ = 3.6 Hz, 1H, H-1′), 4.32 (m, 1H, H-4′), 3.61 (m, 1H, H-5′), 3.52 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 5.4 Hz, 1H, H-8′), 3.46 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 6.2 Hz, 1H, H-8′), 0.81 (s, 9H, C($CH_3$)$_3$), −0.02 (s, 3H, $CH_3$Si), −0.05 (s, 3H, $CH_3$Si); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 151.6 (CH, C-2), 151.1/150.9 (C, C-4/C-6), 144.3 (CH, C-8), 141.1 (CH, C-6′), 137.6 (CH, C-7′), 132.5 (C, C-5), 86.6 (CH, C-2′), 82.7 (CH, C-4′), 64.7 ($CH_2$, C-8′), 53.5 (CH, C-1′), 49.6 (CH, C-5′), 25.8 ($CH_3$, C($CH_3$)$_3$), 18.2 (C, *C*($CH_3$)$_3$), −5.5 ($CH_3$, 2 × $CH_3$Si). Anal. Calcd for ($C_{18}H_{25}ClN_4O_2Si$): C, 55.02; H, 6.41; N, 14.26. Found: C, 55.07; H, 6.46; N, 14.21.

*(1′R,2′R,4′S,5′S)-6-Chloro-9-(4-hydroxymethyl-3-oxabicyclo-[3.2.0]hept-6-en-2-yl)-9H-purine (**30**).* To a solution of **28** (100 mg, 0.25 mmol) in dry THF (3 mL) was added a 1.0 M solution of TBAF in THF (0.51 mL, 0.51 mmol). The reaction was allowed to stir for 2 h, and the solvent was removed. The residue was purified by column chromatography (EtOAc−hexane, 4:1) to give **30** (53 mg, 0.21 mmol, 75% yield) as a white solid: mp 143−145 °C (from EtOAc−pentane); $[\alpha]_D$ −127.1 (*c* 1.40, MeOH); IR (ATR) 3345, 3117, 2954, 1592, 1562, 1397,

1203 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.66 (s, 1H, H-2), 8.43 (s, 1H, H-8), 6.38 (d, $J_{6',7'}$ = 2.9 Hz, 1H, H-6′), 6.35 (d, $J_{2',1'}$ = 5.4 Hz, 1H, H-2′), 5.66 (d, $J_{7',6'}$ = 2.9 Hz, 1H, H-7′), 4.26 (ddd, $J_{4',8'}$ = 5.3 Hz, $J_{4',8'}$ = 4.4 Hz, $J_{4',5'}$ = 0.7 Hz, 1H, H-4'), 3.91 (m, 1H, H-1′), 3.74 (m, $J_{8',4'}$ = 5.8 Hz, $J_{8',4'}$ = 4.3 Hz, 2H, H-8′), 3.50 (m, $J_{5',1'}$ = 3.6 Hz, 1H, H-5′), 3.07 (br s, 1H, OH); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 151.8 (CH, C-2), 150.8/150.7 (C, C-4/C-6), 143.7 (CH, C-8), 142.0 (CH, C-6′), 134.5 (CH, C-7′), 131.4 (C, C-5), 82.9 (CH, C-2′), 77.7 (CH, C-4′), 64.0 ($CH_2$, C-8′), 50.7 (CH, C-1′), 48.7 (CH, C-5′).

*(1′R,2′R,4′S,5′S)-6-Chloro-9-(4-hydroxymethyl-3-oxabicyclo[3.2.0]-hept-6-en-2-yl)-9H-purine (**31**).* To a solution of **29** (99 mg, 0.25 mmol) in THF (3 mL) was added a 1.0 M solution of TBAF in THF (0.50 mL, 0.50 mmol). The reaction was allowed to stir for 2 h, and the solvent was removed. The residue was purified by column chromatography (hexane−EtOAc, 1:4) to give **31** (59 mg, 0.21 mmol, 84% yield) as a white solid: mp 128−129 °C (from EtOAc−pentane); $[\alpha]_D$ −24.0 (*c* 1.00, $CHCl_3$); IR (ATR) 3287, 3112, 3073, 2952, 2900, 2868, 1590, 1555, 1204 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.72 (s, 1H, H-2), 8.54 (s, 1H, H-8), 6.34 (s, 2H, H-6′, H-7′), 6.25 (s, 1H, H-2′), 4.39 (ddd, $J_{4',8'}$ = 5.8 Hz, $J_{4',8'}$ = 3.6 Hz, $J_{4',5'}$ = 1.9 Hz, 1H, H-4′), 4.35 (m, 1H, H-1′), 3.73 (m, 1H, H-5′), 3.66 (dd, $J_{gem}$ = 11.6 Hz, $J_{8',4'}$ = 3.6 Hz, 1H, H-8′), 3.52 (dd, $J_{gem}$ = 11.6 Hz, $J_{8',4'}$ = 5.8 Hz, 1H, H-8′), 3.32 (br s, 1H, OH); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 151.7 (CH, C-2), 151.1/150.6 (C, C-4/C-6), 144.8 (CH, C-8), 141.2 (CH, C-6′), 137.4 (CH, C-7′), 131.7 (C, C-5), 86.0 (CH, C-2′), 82.8 (CH, C-4′), 63.9 ($CH_2$, C-8′), 53.5 (CH, C-1′), 49.4 (CH, C-5′).

*(1′R,2′S,4′S,5′S)-9-(4-Hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-yl)adenine (**32**).* A solution of **30** (19 mg, 0.068 mmol) and saturated $NH_3$/MeOH (4 mL) was heated at 90 °C in a sealed tube for 36 h. After cooling to room temperature the solvent was removed under vacuum, and the residue was purified by column chromatography ($CH_2Cl_2$:MeOH, 9:1) to afford **32** (17 mg, 0.066 mmol, 97% yield) as a white solid: mp 164−166 °C (from ether); $[\alpha]_D$ −84.5 (*c* 1.0, DMSO); IR (ATR) 3359, 3326, 3191, 2933, 1650, 1602 $cm^{-1}$; $^1H$ NMR (360 MHz, $CD_3OD$) $\delta$ 8.24 (s, 1H, H-8), 8.19 (s, 1H, H-2), 6.39 (ddd, $J_{2',1'}$ = 5.4 Hz, 1H, H-2′), 5.70 (ddd, $J_{7',6'}$ = 2.9 Hz, $J_{7',5'}$ = 0.5 Hz, $J_{7',1'}$ = 0.5 Hz, 1H, H-7′), 4.19 (ddd, $J_{4',8'}$ = 4.9 Hz, $J_{4',8'}$ = 4.9 Hz, $J_{4',5'}$ = 1.0 Hz, 1H, H-4′), 3.92 (dddd, $J_{1',2'}$ = 5.1 Hz, $J_{1',5'}$ = 3.6 Hz, $J_{1',6'}$ = 0.6 Hz, $J_{1',7'}$ = 0.6 Hz, 1H, H-1′), 3.66 (d, $J_{8',4'}$ = 4.9 Hz, 2H, H-8′), 3.53 (dddd, $J_{5',1'}$ = 3.6 Hz, $J_{5',4'}$ = 1.1 Hz, $J_{5',6'}$ = 0.6 Hz, $J_{5',7'}$ = 0.6 Hz, 1H, H-5′); $^{13}C$ NMR (90 MHz, $CD_3OD$) $\delta$ 157.3 (C, C-6), 153.9 (C, C-2), 149.8 (C, C-4), 143.2 (CH, C-6′), 140.4 (CH, C-8), 136.0 (CH, C-7′), 120.0 (C, C-5), 84.4 (CH, C-2′), 79.2 (CH, C-4′), 64.7 ($CH_2$, C-8′), 52.3 (CH, C-1′), 50.5 (CH, C-5′). HRMS (ESI+) calcd for $[(C_{12}H_{13}N_5O_2) + H]^+$ 260.1142, found 260.1133.

*(1′R,2′R,4′S,5′S)-9-(4-Hydroxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-yl)adenine (**33**).* A solution of **31** (21 mg, 0.075 mmol) and saturated $NH_3$/MeOH (4 mL) was heated at 90 °C in a sealed tube for 36 h. After cooling to room temperature the solvent was removed under vacuum, and the residue was purified by column chromatography ($CH_2Cl_2$:MeOH, 9:1). Recrystallization with MeOH gave **33** (14 mg, 0.054 mmol, 72% yield) as a white solid: mp 229−231 °C (from MeOH); $[\alpha]_D$ −13.3 (*c* 0.9, DMSO); IR (ATR) 3230, 3117, 3144, 2931, 2820, 1687, 1606, 1569, 1296 $cm^{-1}$; $^1H$ NMR (360 MHz, $CD_3OD$) $\delta$ 8.35 (s, 1H, H-8), 8.20 (s, 1H, H-2), 6.34 (ddd, $J_{7',6'}$ = 2.8 Hz, $J_{7',1'}$ = 0.8 Hz, $J_{7',5'}$ = 0.8 Hz, 1H, H-7′), 6.32 (m, $J_{6',7'}$ = 2.8 Hz, 1H, H-6′), 6.18 (s, 1H, H-2′), 4.36 (ddd, $J_{1',5'}$ = 3.6 Hz, $J_{1',7'}$ = 0.8 Hz, $J_{1',2'}$ = 0.8 Hz, 1H, H-1′), 4.21 (m, 1H, H-4′), 3.68 (m, 1H, H-5′), 3.36 (d, $J_{8',4'}$ = 1.5 Hz, 1H, H-8′), 3.34 (d, $J_{8',4'}$ = 2.2 Hz, 1H, H-8′); $^{13}C$ NMR (90 MHz, $CD_3OD$) $\delta$ 157.3 (C, C-6), 153.7 (CH, C-1), 150.2 (C, C-4), 142.2 (CH, C-6′), 141.3 (CH, C-8), 139.2 (CH, C-7′), 120.6 (C, C-5), 86.5 (CH, C-2′), 83.8 (CH, C-4′), 64.8 ($CH_2$, C-8′), 54.3 (CH, C-1′), 51.3 (CH, C-5′). HRMS (ESI+) calcd for ($[(C_{12}H_{13}N_5O_2) + Na]^+$) 282.0961, found 282.0960.

*(1S,4S,5R)-4-tert-Butyldimethylsilyloxymethyl-1-fluoro-3-oxabicyclo-[3.2.0]heptan-2-one (**15a**).* To a solution of **15** (410 mg, 2.56 mmol) in $CH_2Cl_2$ (18 mL) at 0 °C were successively added imidazole (360 mg, 5.26 mmol) and *tert*-butyldimethylsilyl chloride (536 mg, 3.57 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was successively washed with 5% aqueous citric acid solution (3 × 10 mL), saturated aqueous $NaHCO_3$ solution (3 × 10 mL), and brine (3 × 10 mL). Then, the organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. Purification by column chromatography (hexane−diethyl ether 10:1) afforded **15a** (618 mg, 2.25 mmol, 88% yield) as a white solid: mp 48−49 °C (from diethyl ether); $[\alpha]_D$ −53.0 (*c* 1.0, $CHCl_3$); IR (ATR) 2929, 1780, 1098, 1081, 827 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.37 (ddd, $J_{4,8}$ = 3.6 Hz, $J_{4,F}$ = 3.3 Hz, $J_{4,8}$ = 2.7 Hz, 1H, H-4), 3.81 (dd, $J_{gem}$ = 11.2 Hz, $J_{8,4}$ = 3.6 Hz, 1H, H-8), 3.67 (dd, $J_{gem}$ = 11.2 Hz, $J_{8,4}$ = 2.7 Hz, 1H, H-8), 3.21 (dddd, *J* = 10.6 Hz, *J* = 10.4 Hz, *J* = 6.6 Hz, $J_{5,4}$ = 0.5 Hz, 1H, H-5), 2.59 (m, 1H, H-7exo), 2.50 (m, 1H, H-7endo), 2.32 (m, 1H, H-6exo), 1.52 (m, 1H, H-6endo), 0.87 (s, 9H, $(CH_3)_3C$), 0.06 (s, 3H, $CH_3Si$), 0.05 (s, 3H, $CH_3Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 173.8 (d, $^2J_{C-F}$ = 25.4 Hz, C═O), 90.5 (d, $^1J_{C-F}$ = 243.2 Hz, C, C-1), 83.9 (d, $^3J_{C-F}$ = 2.3 Hz, CH, C-4), 63.8 (s, $CH_2$, C-8), 42.4 (d, $^2J_{C-F}$ = 17.8 Hz, CH, C-5), 29.1 (d, $^2J_{C-F}$ =24.4 Hz, $CH_2$, C-7), 25.7 (s, $CH_3$, $(CH_3)_3C$), 18.2 (s, C, $(CH_3)_3C$), 15.6 (d, $^3J_{C-F}$ = 15.8 Hz, $CH_2$, C-6), −5.7 (s, $CH_3$, $CH_3Si$), −5.8 (s, $CH_3$, $CH_3Si$); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −150.8 to −151.0 (m). HRMS (ESI+) calcd for $[C_{13}H_{23}FO_3Si + H]^+$ 275.1473, found 275.1474.

*(1S,2R,4S,5R)- and (1S,2S,4S,5R)-2-Acetyloxy-4-tert-butyldimethyl-silyloxymethyl-1-fluoro-3-oxabicyclo[3.2.0]heptane (**34** and **35**).* To a solution of **15a** (1.79 g, 6.52 mmol) in dry $CH_2Cl_2$ (30 mL) at −78 °C was added dropwise a 1.0 M solution of DIBAL-H in $CH_2Cl_2$ (9.3 mL, 9.3 mmol). After 2.5 h of stirring at −78 °C, the reaction mixture was quenched by the slow addition of an aqueous $HNO_3$ 3% solution (25 mL) and allowed to warm to room temperature. The two layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness affording a reaction crude which was used in the next reaction without further purification. To an ice-cooled solution of this crude and pyridine (7.4 mL, 92.7 mmol) in $CH_2Cl_2$ (50 mL) was added dropwise acetic anhydride (5.9 mL, 61.8 mmol). The reaction mixture was stirred at room temperature overnight. Then, the reaction was washed with HCl 3% (3 × 20 mL), saturated $NaHCO_3$ solution (3 × 20 mL), and brine (3 × 20 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. The resulting crude residue was purified by column chromatography (hexane−diethyl ether 10:1) to afford a 84:16 mixture of acetates **34** and **35** (1.84 g, 5.78 mmol, 89% yield for the 2 steps). A further column chromatography (from hexane−diethyl ether 20:1 to hexane−diethyl ether 5:1) allowed us to isolate pure α-acetate **34** and β-acetate **35** both as colorless oils.

**34**: $[\alpha]_D$ +22.4 (*c* 1.25, $CHCl_3$); IR (ATR) 2929, 1752, 1222, 1105 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.31 (d, $J_{2,F}$ = 14.5 Hz, 1H, H-2), 4.14 (dddd, $J_{4,8}$ = 5.6 Hz, $J_{4,8}$ = 4.2 Hz, $J_{4,5}$ = 2.1 Hz, $J_{4,F}$ = 2.1 Hz, 1H, H-4), 3.67 (dd, $J_{gem}$ = 10.7 Hz, $J_{8,4}$ = 4.2 Hz, 1H, H-8), 3.61 (dd, $J_{gem}$ = 10.7 Hz, $J_{8,4}$ = 5.6 Hz, 1H, H-8), 3.01 (m, 1H, H-5), 2.40 (m, 1H, H-7endo), 2.30 (m, 1H, H-7exo), 2.15 (m, 4H, H-6exo, $CH_3CO$), 1.50 (m, 1H, H-6endo), 0.89 (s, 9H, $(CH_3)_3C$), 0.06 (s, 3H, $CH_3Si$), 0.05 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 169.5 (s, C═O), 102.8 (d, $^1J_{C-F}$ = 234.2 Hz, C, C-1), 101.0 (d, $^2J_{C-F}$ = 42.0 Hz, CH, C-2), 87.1 (s, CH, C-4), 64.6 (s, $CH_2$, C-8), 45.8 (d, $^2J_{C-F}$ = 18.9 Hz, CH, C-5), 25.9 (d, $^2J_{C-F}$ = 20.2 Hz, $CH_2$, C-7), 25.8 (s, $CH_3$, $(CH_3)_3C$), 21.0 (s, $CH_3$, $CH_3CO$), 18.3 (s, C, $(CH_3)_3C$), 16.3 (d, $^3J_{C-F}$ = 17.4 Hz, $CH_2$, C-6), −5.4 (s, $CH_3$, $CH_3Si$), −5.5 (s, $CH_3$, $CH_3Si$); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −144.1 to −144.4 (m). HRMS (ESI+) calcd for $[C_{15}H_{27}FO_4Si + Na]^+$ 341.1555, found 341.1550.

**35**: $[\alpha]_D$ −78.3 (*c* 0.60, $CHCl_3$); IR (ATR) 2929, 1748, 1229, 1100, 1010 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 6.18 (s, 1H, H-2), 4.05 (ddd, $J_{4,8}$ = 8.4 Hz, $J_{4,8}$ = 5.7 Hz, $J_{4,F}$ = 3.0 Hz, 1H, H-4), 3.71 (dd, $J_{gem}$ = 10.2 Hz, $J_{8,4}$ = 5.7 Hz, 1H, H-8), 3.56 (dd, $J_{gem}$ = 10.2 Hz, $J_{8,4}$ = 8.4 Hz, 1H, H-8), 3.01 (m, 1H, H-5), 2.49 (m, 1H, H-7exo), 2.36 (m, 1H,

H-7endo), 2.24 (m, 1H, H-6exo), 2.08 (s, 3H, $CH_3CO$), 1.50 (m, 1H, H-6endo), 0.88 (s, 9H, $(CH_3)_3C$), 0.07 (s, 3H, $CH_3Si$), 0.06 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 169.7 (s, C=O), 99.2 (d, $^1J_{C-F}$ = 243.7 Hz, C, C-1), 99.3 (d, $^2J_{C-F}$ = 18.2 Hz, CH, C-2), 87.4 (d, $^3J_{C-F}$ = 2.8 Hz, CH, C-4), 64.5 (s, $CH_2$, C-8), 44.2 (d, $^2J_{C-F}$ = 19.4 Hz, CH, C-5), 28.7 (d, $^2J_{C-F}$ = 23.9 Hz, $CH_2$, C-7), 25.9 (s, $CH_3$, $(CH_3)_3C$), 21.2 (s, $CH_3$, $CH_3CO$), 18.3 (s, C, $(CH_3)_3C$), 16.9 (d, $^3J_{C-F}$ = 12.7 Hz, $CH_2$, C-6), −5.3 (s, $CH_3$, $CH_3Si$), −5.4 (s, $CH_3$, $CH_3Si$); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −155.7 to −155.9 (m). HRMS (ESI+) calcd for $[C_{15}H_{27}FO_4Si + Na]^+$ 341.1555, found 341.1542.

*(1S,4S,5R)-4-tert-Butyldimethylsilyloxymethyl-1-chloro-3-oxabicyclo[3.2.0]heptan-2-one (**17a**).* To a solution of **17** (490 mg, 2.77 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C were successively added imidazole (390 mg, 5.7 mmol) and *tert*-butyldimethylsilyl chloride (580 mg, 3.87 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was successively washed with 5% aqueous citric acid solution (3 × 10 mL), saturated aqueous $NaHCO_3$ solution (3 × 10 mL), and brine (3 × 10 mL). Then, the organic layer was dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness affording 750 mg of a reaction crude which was used in the next reaction without further purification due to its instability. However, a small sample was purified allowing its complete characterization: $[\alpha]_D$ −6.7 (*c* 1.1, $CHCl_3$); IR (ATR) 2927, 2855, 1766, 834, 778 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.37 (t, $J_{4,8}$ = 4.6 Hz, 1H, H-4), 3.73 (d, $J_{8,4}$ = 4.6 Hz, 2H, H-8), 3.28 (dd, *J* = 8.9 Hz, *J* = 6.6 Hz, 1H, H-5), 2.71−2.45 (m, 3H, H-6, 2H-7), 1.83 (m, 1H, H-6), 0.89 (s, 9H, $(CH_3)_3C$), 0.07 (s, 6H, $2CH_3Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 175.3 (C=O, C-2), 84.1 (CH, C-4), 63.6 ($CH_2$, C-8), 59.6 (C, C-1), 45.7 (CH, C-5), 33.8 ($CH_2$, C-7), 25.8 ($CH_3$, $CH_3CO$), 20.3 ($CH_2$, C-6), 18.4 (C, $(CH_3)_3C$), −3.7 ($CH_3$, $CH_3Si$), −3.7 (s, $CH_3$, $CH_3Si$). HRMS (ESI+) calcd for $[C_{13}H_{23}ClO_3Si + Na]^+$ 313.0997, found 313.0991.

*(1S,2R,4S,5R)-2-Acetyloxy-4-tert-butyldimethylsilyloxymethyl-1-chloro-3-oxabicyclo[3.2.0] heptane (**36**).* To a solution of crude **17a** (750 mg, 2.57 mmol) in dry $CH_2Cl_2$ (10 mL) at −78 °C was added dropwise a 1.0 M solution of DIBAL-H in $CH_2Cl_2$ (4.9 mL, 4.9 mmol). After 3.5 h of stirring at −78 °C, the reaction mixture was quenched by the slow addition of a $HNO_3$ 3% solution (9 mL) and allowed to warm to room temperature. The two layers were separated, and the aqueous was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness affording a reaction crude which was used in the next reaction without further purification. To an ice-cooled solution of this crude and pyridine (2.8 mL, 36.1 mmol) in $CH_2Cl_2$ (25 mL) was added dropwise acetic anhydride (2.1 mL, 19.0 mmol). The reaction mixture was stirred at room temperature overnight. Then, the reaction was washed with HCl 3% (3 × 15 mL), saturated aqueous $NaHCO_3$ solution (3 × 15 mL), and brine (3 × 15 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. The crude residue was purified by column chromatography (hexane−diethyl ether 10:1) to afford the α-acetate **36** (758 mg, 2.26 mmol, 82% yield over 3 steps) as a colorless oil: $[\alpha]_D$ +45.7 (*c* 1.40, $CHCl_3$); IR (ATR) 2929, 1751, 1221 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.37 (s, 1H, H-2), 4.15 (ddd, $J_{4,8}$ = 6.0 Hz, $J_{4,8}$ = 4.6 Hz, $J_{4,5}$ = 2.4 Hz, 1H, H-4), 3.69 (dd, $J_{gem}$ = 10.6 Hz, $J_{8,4}$ = 4.6 Hz, 1H, H-8), 3.62 (dd, $J_{gem}$ = 10.6 Hz, $J_{8,4}$ = 6.0 Hz, 1H, H-8), 3.08 (m, 1H, H-5), 2.62 (m, 1H, H-7endo), 2.37 (m, 2H, H-7exo, H-6exo), 2.15 (s, 3H, $CH_3CO$), 1.74 (m, 1H, H-6endo), 0.89 (s, 9H, $(CH_3)_3C$), 0.08 (s, 3H, $CH_3Si$), 0.07 (s, 3H, $CH_3Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 169.5 (C=O), 103.8 (CH, C-2), 87.2 (CH, C-4), 71.1 (C, C-1), 64.4 ($CH_2$, C-8), 49.7 (CH, C-5), 30.2 ($CH_2$, C-7), 25.9 ($CH_3$, $(CH_3)_3C$), 21.1 ($CH_3$, $CH_3CO$), 20.9 ($CH_2$, C-6), 18.3 (C, $(CH_3)_3C$), −5.4 ($CH_3$, $CH_3Si$), −5.4 ($CH_3$, $CH_3Si$). HRMS (ESI+) calcd for $[C_{15}H_{27}ClO_4Si + Na]^+$ 357.1259, found 357.1245.

*(1′S,2′S,4′S,5′R)- and (1′S,2′R,4′S,5′R)-6-Chloro-9-(4′-tert-butyldimethylsilyloxymethyl-1′-fluoro-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-purine (**37** and **38**) and (1′S,2′S,4′S,5′R)- and (1′S,2′R,4′S,5′R)-6-Chloro-7-(4′-tert-butyldimethylsilyloxymethyl-1′-fluoro-3′-oxabicyclo [3.2.0] hept-2-yl)-7H-purine (**39** and **40**).* BSA (567 μL, 2.10 mmol) was added to a suspension of 6-chloropurine (172 mg, 1.10 mmol) in dry toluene (4 mL) under argon atmosphere. The reaction was stirred for 20 min and cooled to 0 °C. Then, a solution of a mixture of **34** and **35** (245 mg, 0.77 mmol) in dry toluene (2 mL) and TMSOTf (175 μL, 0.95 mmol) was successively added, and the reaction mixture was stirred at 100 °C for 1 h. Then, after allowing the solution to cool to room temperature, $CH_2Cl_2$ (10 mL) was added, and the reaction was quenched with aqueous saturated $NaHCO_3$ (4 mL). The two layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. The crude residue was purified by column chromatography (from hexane−EtOAc 10:1 to hexane−EtOAc 2:1) to afford the following fractions: (i) **37** (161 mg, 0.39 mmol, 53% yield) as a white solid; (ii) **38** (94 mg, 0.23 mmol, 30% yield) as a colorless oil; (iii) **39** (9 mg, 0.02 mmol, 3% yield) as a colorless oil; and (iv) **40** (9 mg, 0.02 mmol, 3% yield) as a yellow solid.

**37**: Mp decomposes over 60 °C (from hexane−EtOAc); $[\alpha]_D$ −13.8 (*c* 1.60, $CHCl_3$); IR (ATR) 3108, 2928, 1588, 1561, 1090 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.77 (s, 1H, H-2), 8.42 (s, 1H, H-8), 6.63 (d, $J_{2',F}$ = 15.6 Hz, 1H, H-2′), 4.33 (ddd, $J_{4',F}$ = 4.3 Hz, $J_{4',8'}$ = 4.1 Hz, $J_{4',8'}$ = 3.5 Hz, 1H, H-4′), 3.86 (dd, $J_{gem}$ = 10.9 Hz, $J_{8',4'}$ = 4.1 Hz, 1H, H-8′), 3.74 (dd, $J_{gem}$ = 10.9 Hz, $J_{8',4'}$ = 3.5 Hz, 1H, H-8′), 3.33 (m, 1H, H-5′), 2.29 (m, 2H, H-6′exo, H-7′exo), 1.59 (m, 1H, H-7′endo), 1.48 (m, 1H, H-6′endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.11 (s, 3H, $CH_3Si$), 0.10 (s, 3H, $CH_3Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 152.4 (s, CH, C-2), 151.1 (2s, 2C, C-4/C-6), 142.6 (s, CH, C-8), 132.0 (s, C, C-5), 101.9 (d, $^1J_{C-F}$ = 238.5 Hz, C, C-1′), 91.6 (d, $^2J_{C-F}$ = 40.7 Hz, CH, C-2′), 86.1 (d, $^3J_{C-F}$ = 2.0 Hz, CH, C-4′), 65.1 (s, $CH_2$, C-8′), 45.9 (d, $^2J_{C-F}$ = 18.8 Hz, CH, C-5′), 25.8 (s, $CH_3$, $(CH_3)_3C$), 25.7 (d, $^2J_{C-F}$ = 24.6 Hz, $CH_2$, C-7′), 18.3 (s, C, $(CH_3)_3C$), 16.1 (d, $^3J_{C-F}$ = 15.5 Hz, $CH_2$, C-6′), −5.5 (s, $CH_3$, $2CH_3Si$); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −142.7 to −143.1 (m). HRMS (ESI+) calcd for $[C_{18}H_{26}ClFN_4O_2Si + Na]^+$ 435.1390, found 435.1379.

**38**: $[\alpha]_D$ −16.0 (*c* 0.50, $CHCl_3$); IR (ATR) 3128, 2929, 1702, 1590, 1097 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.73 (s, 1H, H-2), 8.54 (d, $J_{8,F}$ = 2.7 Hz, 1H, H-8), 6.58 (d, $J_{2',F}$ = 11.5 Hz, 1H, H-2′), 4.21 (ddd, $J_{4',F}$ = 5.6 Hz, $J_{4',8'}$ = 3.6 Hz, $J_{4',8'}$ = 3.6 Hz, 1H, H-4′), 3.87 (dd, $J_{gem}$ = 11.2 Hz, $J_{8',4'}$ = 3.6 Hz, 1H, H-8′), 3.74 (dd, $J_{gem}$ = 11.2 Hz, $J_{8',4'}$ = 3.6 Hz, 1H, H-8′), 3.28 (m, 1H, H-5′), 2.58 (m, 1H, H-7′endo), 2.50 (m, 1H, H-7′exo), 2.36 (m, 1H, H-6′exo), 1.62 (m, 1H, H-6′endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, $CH_3Si$), 0.11 (s, 3H, $CH_3Si$); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 152.0 (s, CH, C-2), 151.6/150.9 (2s, 2C, C-4/C-6), 144.9 (d, $^4J_{C-F}$ = 4.6 Hz, CH, C-8), 131.4 (s, C, C-5), 98.0 (d, $^1J_{C-F}$ = 250.6 Hz, C, C-1′), 89.3 (d, $^2J_{C-F}$ = 17.8 Hz, CH, C-2′), 85.8 (s, CH, C-4′), 64.5 (s, $CH_2$, C-8′), 47.2 (d, $^2J_{C-F}$ = 18.7 Hz, CH, C-5′), 28.6 (d, $^2J_{C-F}$ = 22.8 Hz, $CH_2$, C-7′), 25.9 (s, $CH_3$, $(CH_3)_3C$), 18.4 (s, C, $(CH_3)_3C$), 16.6 (d, $^3J_{C-F}$ = 18.2 Hz, $CH_2$, C-6′), −5.4 (s, $CH_3$, $2CH_3Si$); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −145.7 to −146.0 (m). HRMS (ESI+) calcd for $[C_{18}H_{26}ClFN_4O_2Si + Na]^+$ 435.1390, found 435.1377.

**39**: Mp 61−63 °C (from EtOAc); $[\alpha]_D$ −63.1 (*c* 1.60, $CHCl_3$); IR (ATR) 2927, 1377, 1254, 1099 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.89 (s, 1H, H-2), 8.69 (s, 1H, H-8), 6.98 (d, $J_{2',F}$ = 14.0 Hz, 1H, H-2′), 4.39 (ddd, $J_{4',8'}$ = 3.5 Hz, $J_{4',F}$ = 3.3 Hz, $J_{4',8'}$ = 3.0 Hz, 1H, H-4′), 3.90 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 3.5 Hz, 1H, H-8′), 3.73 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 3.0 Hz, 1H, H-8′), 3.23 (m, 1H, H-5′), 2.28 (m, 2H, H-6′exo, H-7′exo), 1.47 (m, 1H, H-7′endo), 1.39 (m, 1H, H-6′endo), 0.92 (s, 9H, $(CH_3)_3C$), 0.11 (s, 3H, $CH_3Si$), 0.10 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 162.2 (s, C, C-4), 152.6 (s, CH, C-2), 146.1 (s, CH, C-8), 143.2 (s, C, C-6), 121.8 (s, C, C-5), 101.9 (d, $^1J_{C-F}$ = 240.0 Hz, C, C-1′), 93.1 (d, $^2J_{C-F}$ = 38.7 Hz, CH, C-2′), 86.4 (d, $^3J_{C-F}$ = 1.7 Hz, CH, C-4′), 65.5 (s, $CH_2$, C-8′), 46.0 (d, $^2J_{C-F}$ = 19.0 Hz, CH, C-5′), 25.8 (s, $CH_3$, $(CH_3)_3C$), 25.5 (d, $^2J_{C-F}$ = 23.3 Hz, $CH_2$, C-7′), 18.3 (s, C, $(CH_3)_3C$), 16.4 (d, $^3J_{C-F}$ = 15.6 Hz, $CH_2$, C-6′), −5.5 (s, $CH_3$, $2CH_3Si$); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −142.5 to −142.6 (m). HRMS (ESI+) calcd for $[C_{18}H_{26}ClFN_4O_2Si + Na]^+$ 435.1390, found 435.1374.

**40**: $[\alpha]_D$ +41.8 (*c* 1.10, $CHCl_3$); IR (ATR) 2928, 1599, 1536, 1257, 838 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.89 (d, $J_{8,F}$ = 1.6 Hz, 1H, H-8), 8.87 (d, $J_{2,F}$ = 1.2 Hz, 1H, H-2), 6.80 (d, $J_{2',F}$ = 8.2 Hz, 1H, H-2′), 4.27 (ddd, $J_{4',F}$ = 5.5 Hz, $J_{4',8'}$ = 4.2 Hz, $J_{4',8'}$ = 3.2 Hz, 1H, H-4′), 3.92 (dd, $J_{gem}$ = 11.5 Hz, $J_{8',4'}$ = 3.2 Hz, 1H, H-8′), 3.72 (dd, $J_{gem}$ = 11.5 Hz, $J_{8',4'}$ = 4.2 Hz, 1H, H-8′), 3.22 (m, 1H, H-5′), 2.68 (m, 1H, H-7′endo), 2.59 (m, 1H, H-7′exo), 2.36 (m, 1H, H-6′exo), 1.62 (m, 1H, H-6′endo), 0.91 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, $CH_3Si$), 0.09 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 162.4 (s, C, C-4), 152.2 (s, CH, C-2), 148.4 (d, $^4J_{C-F}$ = 2.4 Hz, CH, C-8), 141.7 (s, C, C-6), 121.9 (s, C, C-5), 99.1 (d, $^1J_{C-F}$ = 249.7 Hz, C, C-1′), 91.7 (d, $^2J_{C-F}$ = 18.1 Hz, CH, C-2′), 86.5 (s, CH, C-4′), 64.3 (s, $CH_2$, C-8′), 46.7 (d, $^2J_{C-F}$ = 19.1 Hz, CH, C-5′), 29.2 (d, $^2J_{C-F}$ = 23.0 Hz, $CH_2$, C-7′), 25.8 (s, $CH_3$, $(CH_3)_3C$), 18.3 (s, C, $(CH_3)_3C$), 16.3 (d, $^3J_{C-F}$ = 16.7 Hz, $CH_2$, C-6′), −5.5 (s, $CH_3$, $2CH_3Si$); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −146.1 to −146.3 (m). HRMS (ESI+) calcd for $[C_{18}H_{26}ClFN_4O_2Si + Na]^+$ 435.1390, found 435.1383.

*(1′S,2′S,4′S,5′R)- and (1′S,2′R,4′S,5′R)-6-Chloro-9-(4′-tert-butyldimethylsilyloxymethyl-1′-chloro-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-purine (**41** and **42**) and (1′S,2′S,4′S,5′R)- and (1′S,2′R,4′S,5′R)-6-Chloro-7-(4′-tert-butyldimethylsilyloxymethyl-1′-chloro-3′-oxabicyclo[3.2.0]hept-2-yl)-7H-purine (**43** and **44**).* BSA (147 μL, 0.57 mmol) was added to a suspension of 6-chloropurine (44 mg, 0.29 mmol) in dry acetonitrile (2 mL) under an argon atmosphere. The reaction was stirred for 20 min and cooled to 0 °C. Then, a solution of **36** (63 mg, 0.19 mmol) in dry acetonitrile (1.5 mL) and TMSOTf (45 μL, 0.25 mmol) was successively added, and the reaction mixture was stirred at 82 °C for 1 h. Then $CH_2Cl_2$ (5 mL) was added, and the reaction was quenched with aqueous saturated $NaHCO_3$ (3 mL), after allowing the solution to cool to room temperature. The mixture was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered, and evaporated to dryness. The crude residue was purified by column chromatography (from hexane−EtAcO 14:1 to hexane−EtAcO 1:1) to afford the following fractions: (i) **42** (10 mg, 0.02 mmol, 12% yield) as a colorless oil; (ii) **41** (57 mg, 0.13 mmol, 70% yield) as a white solid; (iii) **43** (4 mg, 0.01 mmol, 5% yield) as a colorless oil; and (iv) **44** (6 mg, 0.02 mmol, 8% yield) as a colorless oil.

**41**: Mp decomposes over 70 °C (from hexane−EtAcO); $[\alpha]_D$ +17.2 (*c* 2.5, $CHCl_3$); IR (ATR) 3112, 2949, 2854, 1590, 1561, 1099 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.79 (s, 1H, H-2), 8.45 (s, 1H, H-8), 6.72 (s, 1H, H-2′), 4.34 (ddd, $J_{4',8'}$ = 4.7 Hz, $J_{4',8'}$ = 4.1 Hz, $J_{4',5'}$ = 1.0 Hz, 1H, H-4′), 3.85 (dd, $J_{gem}$ = 10.9 Hz, $J_{8',4'}$ = 4.7 Hz, 1H, H-8′), 3.77 (dd, $J_{gem}$ = 10.9 Hz, $J_{8',4'}$ = 4.1 Hz, 1H, H-8′), 3.29 (ddd, $J_{5',6'}$ = 8.2 Hz, $J_{5',6'}$ = 5.8 Hz, $J_{5',4'}$ = 1.0 Hz, 1H, H-5′), 2.55 (m, 1H, H-6'exo), 2.33 (m, 1H, H-7′exo), 2.12 (m, 1H, H-7′endo), 1.82 (m, 1H, H-6′endo), 0.94 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, $CH_3Si$), 0.12 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 152.4 (CH, C-2), 151.4/151.1 (2C, C-4/C-6), 142.7 (CH, C-8), 131.8 (C, C-5), 93.8 (CH, C-2′), 86.3 (CH, C-4′), 70.5 (C, C-1′), 64.7 ($CH_2$, C-8′), 49.7 (CH, C-5′), 29.7 ($CH_2$, C-7′), 25.9 ($CH_3$, $(CH_3)_3C$), 20.2 ($CH_2$, C-6′), 18.4 (C, $(CH_3)_3C$), −5.4 (s, $CH_3$, $2CH_3Si$). HRMS (ESI+) calcd for $[C_{18}H_{26}Cl_2N_4O_2Si+Na]^+$ 451.1094, found 451.1094.

**42**: $[\alpha]_D$ −30.0 (*c* 0.90, $CHCl_3$); IR (ATR) 2928, 2856, 1589, 1561, 1215 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.71 (s, 1H, H-2), 8.50 (s, 1H, H-8), 6.63 (s, 1H, H-2′), 4.25 (ddd, $J_{4',8'}$ = 4.5 Hz, $J_{4',8'}$ = 4.5 Hz, $J_{4',5'}$ = 2.9 Hz, 1H, H-4′), 3.86 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 4.5 Hz, 1H, H-8′), 3.80 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 4.5 Hz, 1H, H-8′), 3.31 (m, 1H, H-5′), 2.91 (m, 1H, H-7′endo), 2.61 (m, 2H, H-6′exo, H-7′exo), 1.97 (m, 1H, H-6′endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.13 (s, 3H, $CH_3Si$), 0.12 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 152.1 (CH, C-2), 151.2/150.8 (2C, C-4/C-6), 144.0 (CH, C-8), 131.6 (C, C-5), 91.9 (CH, C-2′), 86.4 (CH, C-4′), 71.7 (C, C-1′), 61.6 ($CH_2$, C-8′), 50.8 (CH, C-5′), 33.8 ($CH_2$, C-7′), 25.9 ($CH_3$, $(CH_3)_3C$), 21.5 ($CH_2$, C-6′), 18.4 (C, $(CH_3)_3C$), −5.3 (s, $CH_3$, $CH_3Si$), −5.4 (s, $CH_3$, $CH_3Si$). HRMS (ESI+) calcd for $[C_{18}H_{26}Cl_2N_4O_2Si + Na]^+$ 451.1094, found 451.1083.

**43**: $[\alpha]_D$ −36.8 (*c* 1.25, $CHCl_3$); IR (ATR) 2928, 2856, 1680, 1094 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.91 (s, 1H, H-2), 8.68 (s, 1H, H-8), 7.00 (s, 1H, H-2′), 4.37 (ddd, $J_{4',8'}$ = 3.9 Hz, $J_{4',8'}$ = 3.6 Hz, $J_{4',5'}$ = 1.1 Hz, 1H, H-4′), 3.90 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 3.9 Hz, 1H, H-8′), 3.76 (dd, $J_{gem}$ = 11.0 Hz, $J_{8',4'}$ = 3.6 Hz, 1H, H-8′), 3.30 (ddd, $J_{5',6'}$ = 8.2 Hz, $J_{5',6'}$ = 5.8 Hz, $J_{5',4'}$ = 1.1 Hz, 1H, H-5′), 2.58 (m, 1H, H-6′exo), 2.36 (m, 1H, H-7′exo), 2.12 (m, 1H, H-7′endo), 1.78 (m, 1H, H-6′endo), 0.93 (s, 9H, $(CH_3)_3C$), 0.12 (s, 3H, $CH_3Si$), 0.12 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 162.1 (C, C-4), 152.7 (CH, C-2), 146.4 (CH, C-8), 143.1 (C, C-6), 122.1 (C, C-5), 94.3 (CH, C-2′), 86.6 (CH, C-4′), 70.8 (C, C-1′), 65.3 ($CH_2$, C-8′), 49.8 (CH, C-5′), 30.1 ($CH_2$, C-7′), 26.0 ($CH_3$, $(CH_3)_3C$), 20.7 ($CH_2$, C-6′), 18.4 (C, $(CH_3)_3C$), −5.4 ($CH_3$, $2CH_3Si$). HRMS (ESI+) calcd for $[C_{18}H_{26}Cl_2N_4O_2Si + Na]^+$ 451.1094, found 451.1091.

**44**: $[\alpha]_D$ +52.5 (*c* 0.40, $CHCl_3$); IR (ATR) 2928, 2856, 1252, 1052 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.91 (s, 1H, H-8), 8.89 (s, 1H, H-2), 6.90 (s, 1H, H-2′), 4.31 (ddd, $J_{4',8'}$ = 4.6 Hz, $J_{4',8'}$ = 3.7 Hz, $J_{4',5'}$ = 3.1 Hz, 1H, H-4′), 3.94 (dd, $J_{gem}$ = 11.3 Hz, $J_{8',4'}$ = 3.7 Hz, 1H, H-8′), 3.80 (dd, $J_{gem}$ = 11.3 Hz, $J_{8',4'}$ = 4.6 Hz, 1H, H-8′), 3.28 (m, 1H, H-5′), 2.98 (m, 1H, H-7′endo), 2.73 (m, 1H, H-7′exo), 2.59 (m, 1H, H-6′exo), 1.92 (m, 1H, H-6′endo), 0.90 (s, 9H, $(CH_3)_3C$), 0.15 (s, 3H, $CH_3Si$), 0.14 (s, 3H, $CH_3Si$); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 162.4 (C, C-4), 152.4 (CH, C-2), 147.7 (CH, C-8), 142.0 (C, C-6), 122.0 (C, C-5), 93.9 (CH, C-2′), 87.1 (CH, C-4′), 72.9 (C, C-1′), 63.8 ($CH_2$, C-8′), 50.7 (CH, C-5′), 34.5 ($CH_2$, C-7′), 26.0 ($CH_3$, $(CH_3)_3C$), 20.6 ($CH_2$, C-6′), 18.4 (C, $(CH_3)_3C$), −5.3 ($CH_3$, $2CH_3Si$). HRMS (ESI+) calcd for $[C_{18}H_{26}Cl_2N_4O_2Si + Na]^+$ 451.1094, found 451.1089.

*(1′S,2′S,4′S,5′R)-6-Chloro-9-(1′-fluoro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-purine (**45**).* To an ice-cooled solution of **37** (80 mg, 0.19 mmol) in THF (5 mL) was added $Et_3N \cdot 3HF$ (47 μL, 0.29 mmol), and the resulting solution was stirred for 5 h at room temperature. Then, more $Et_3N \cdot 3HF$ (47 μL, 0.29 mmol) was added, and after 24 h of stirring at room temperature, the solvent was removed. The residue was purified by column chromatography (EtOAc−hexane 2:1) to afford **45** (52 mg, 0.17 mmol, 90% yield) as a white solid: mp 123−126 °C (from $CHCl_3$); $[\alpha]_D$ −13.3 (*c* 1.05, $CHCl_3$); IR (ATR) 3373, 2938, 1590, 1562, 1206, 1034 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.78 (s, 1H, H-2), 8.44 (s, 1H, H-8), 6.64 (dd, $J_{2',F}$ = 15.9 Hz, *J* = 0.9 Hz, 1H, H-2′), 4.45 (ddd, *J* = 5.1 Hz, *J* = 5.0 Hz, *J* = 4.8 Hz, 1H, H-4′), 3.83 (m, 2H, H-8′), 3.19 (m, 1H, H-5′), 2.32 (m, 2H, H-6′exo, H-7′exo), 2.16 (t, $J_{OH,8'}$ = 5.3 Hz, 1H, OH), 1.61 (m, 1H, H-7′endo), 1.53 (m, 1H, H-6′endo); $^{13}C$ NMR (90 MHz, $CDCl_3$) $\delta$ 152.5 (s, CH, C-2), 151.3/150.9 (2s, 2C, C-4/C-6), 142.5 (s, CH, C-8), 131.9 (s, C, C-5), 103.2, 101.9 (d, $^1J_{C-F}$ = 283.2 Hz, C, C-1′), 91.2 (d, $^2J_{C-F}$ = 41.2 Hz, CH, C-2′), 86.1 (d, $^3J_{C-F}$ = 1.3 Hz, CH, C-4′), 63.8 (s, $CH_2$, C-8′), 45.6 (d, $^2J_{C-F}$ = 18.7 Hz, CH, C-5′), 25.6 (d, $^2J_{C-F}$ = 23.2 Hz, $CH_2$, C-7′), 15.9 (d, $^3J_{C-F}$ = 15.7 Hz, $CH_2$, C-6′); $^{19}F$ NMR (235 MHz, $CDCl_3$) $\delta$ −142.1 to −142.4 (m). HRMS (ESI+) calcd for $[C_{12}H_{12}ClFN_4O_2 + Na]^+$ 321.0525, found 321.0530.

*(1′S,2′R,4′S,5′R)-6-Chloro-9-(1′-fluoro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-purine (**46**).* To an ice-cooled solution of **38** (54 mg, 0.13 mmol) in THF (3 mL) was added $Et_3N \cdot 3HF$ (65 μL, 0.39 mmol), and the resulting solution was stirred for 7 h at room temperature. Then, more $Et_3N \cdot 3HF$ (65 μL, 0.39 mmol) was added, and after 24 h of stirring at room temperature, the solvent was removed. The residue was purified by column chromatography (EtOAc−hexane 2:1) to give **46** (35 mg, 0.12 mmol, 90% yield) as a white solid: mp 283−287 °C (from $CHCl_3$); $[\alpha]_D$ −16.7 (*c* 0.90, MeOH); IR (ATR) 3313, 2924, 1592, 1562, 1204, 1141 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 8.75 (s, 1H, H-2), 8.41 (d, $J_{8,F}$ = 2.0 Hz, 1H, H-8), 6.47 (d, $J_{2',F}$ = 12.2 Hz, 1H, H-2′), 4.30 (ddd, $J_{4',F}$ = 5.7 Hz, $J_{4',8'}$ = 4.4 Hz, $J_{4',5'}$ = 2.4 Hz, 1H, H-4′), 3.96 (dd, $J_{gem}$ = 12.2 Hz, $J_{8',4'}$ = 2.4 Hz, 1H, H-8′), 3.74 (dd, $J_{gem}$ = 12.2 Hz, $J_{8',4'}$ = 4.4 Hz, 1H, H-8′), 3.41 (m, 1H, H-5′), 2.56 (m, 2H, H-7′exo, H-7′endo), 2.41 (m, 1H, H-6′exo), 1.63 (m,

1H, H-6′endo); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 151.9 (s, CH, C-2), 151.6/151.5 (2s, 2C, C-4/C-6), 144.6 (d, $^4J_{C-F}$ = 3.3 Hz, CH, C-8), 132.0 (s, C, C-5), 98.4 (d, $^1J_{C-F}$ = 250.6 Hz, C, C-1′), 90.9 (d, $^2J_{C-F}$ = 18.1 Hz, CH, C-2′), 86.3 (s, CH, C-4′), 63.9 (s, $CH_2$, C-8′), 46.8 (d, $^2J_{C-F}$ = 18.6 Hz, CH, C-5′), 28.6 (d, $^2J_{C-F}$ = 22.9 Hz, $CH_2$, C-7′), 16.5 (d, $^3J_{C-F}$ = 17.8 Hz, $CH_2$, C-6′); $^{19}$F NMR (235 MHz, $CDCl_3$) $\delta$ −146.0 to −146.2 (m). HRMS (ESI+) calcd for $[C_{12}H_{12}ClFN_4O_2 + Na]^+$ 321.0525, found 321.0522. Anal. Calcd for ($C_{12}H_{12}ClFN_4O_2$): C, 48.25; H, 4.05; N, 18.76. Found: C, 48.12; H, 4.18; N, 18.62.

*(1′S,2′S,4′S,5′R)-9-(1′-Fluoro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-adenine (**49**).* A solution of **45** (20 mg, 0.07 mmol) and saturated $NH_3$/MeOH (4 mL) was heated at 90 °C in a sealed tube for 40 h. After cooling at room temperature, the solvent was removed under vacuum, and the residue was purified by column chromatography ($CH_2Cl_2$−MeOH 10:1) to furnish **49** (17 mg, 0.06 mmol, 89% yield) as a white solid: mp 210−213 °C (from MeOH); $[\alpha]_D$ −45.7 (*c* 0.35, MeOH); IR (ATR) 3326, 3214, 2920, 2852, 1651, 1600, 1080, 1015 cm$^{-1}$; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 8.41 (s, 1H, H-8), 8.14 (s, 1H, H-2), 7.34 (br s, 2H, $NH_2$), 6.48 (d, $J_{2',F}$ = 16.7 Hz, 1H, H-2′), 5.05 (t, $J_{OH,8'}$ = 5.6 Hz, $J_{OH,8'}$ = 5.0 Hz, 1H, OH), 4.27 (t, *J* = 5.0 Hz, 1H, H-4′), 3.54 (m, 2H, H-8′), 3.57 (m, 1H, H-5′), 2.18 (m, 2H, H-6′exo, H-7′exo), 1.59 (m, 2H, H-6′endo, H-7′endo); $^{13}$C NMR (90 MHz, DMSO-$d_6$) $\delta$ 155.9 (s, C, C-6), 152.8 (s, CH, C-2), 148.9 (s, C, C-4), 138.1 (s, CH, C-8), 118.7 (s, C, C-5), 102.0 (d, $^1J_{C-F}$ = 235.4 Hz, C, C-1′), 89.8 (d, $^2J_{C-F}$ = 40.8 Hz, CH, C-2′), 85.1 (s, CH, C-4′), 62.6 (s, $CH_2$, C-8′), 45.2 (d, $^2J_{C-F}$ = 18.1 Hz, CH, C-5′), 25.2 (d, $^2J_{C-F}$ = 23.0 Hz, $CH_2$, C-7′), 14.9 (d, $^3J_{C-F}$ = 16.5 Hz, $CH_2$, C-6′); $^{19}$F NMR (235 MHz, DMSO-$d_6$) $\delta$ −140.3 to −140.6 (m). HRMS (ESI+) calcd for $[C_{12}H_{14}FN_5O_2 + H]^+$ 280.1204, found 280.1202.

*(1′S,2′R,4′S,5′R)-9-(1′-Fluoro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-adenine (**50**).* A solution of **46** (26 mg, 0.06 mmol) and saturated $NH_3$/MeOH (4 mL) was heated at 90 °C in a sealed tube for 40 h. After cooling at room temperature, the solvent was removed under vacuum, and the residue was purified by column chromatography ($CH_2Cl_2$−MeOH, 13:1) to afford **50** (18 mg, 0.06 mmol, 75% yield) as a white solid: mp 248−251 °C (from MeOH); $[\alpha]_D$ −5.7 (*c* 0.35, MeOH); IR (ATR) 3328, 3104, 2926, 1726, 1606, 1300, 1081, 1014 cm$^{-1}$; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 8.28 (d, $J_{8,F}$ = 2.4 Hz, 1H, H-8), 8.15 (s, 1H, H-2), 7.32 (br s, 2H, $NH_2$), 6.50 (d, $J_{2',F}$ = 12.2 Hz, 1H, H-2′), 5.26 (t, $J_{OH,8'}$ = 5.1 Hz, $J_{OH,8'}$ = 4.8 Hz, 1H, OH), 4.16 (ddd, $J_{4',8'}$ = 5.4 Hz, $J_{4',8'}$ = 4.2 Hz, $J_{4',F}$ = 2.2 Hz, 1H, H-4′), 3.61 (ddd, $J_{gem}$ = 11.7 Hz, $J_{8',OH}$ = 4.8 Hz, $J_{8',4'}$ = 4.2 Hz, 1H, H-8′), 3.52 (ddd, $J_{gem}$ = 11.7 Hz, $J_{8',4'}$ = 5.4 Hz, $J_{8',OH}$ = 5.1 Hz, 1H, H-8′), 3.24 (m, 1H, H-5′), 2.45 (m, 1H, H-7′exo), 2.34 (m, 1H, H-7′endo), 2.23 (m, 1H, H-6′exo), 1.62 (m, 1H, H-6′endo); $^{13}$C NMR (90 MHz, DMSO-$d_6$) $\delta$ 155.9 (s, C, C-6), 152.6 (s, CH, C-2), 149.1 (s, C, C-4), 139.4 (d, $^4J_{C-F}$ = 3.4 Hz, CH, C-8), 118.2 (s, C, C-5), 98.1 (d, $^1J_{C-F}$ = 247.6 Hz, C, C-1′), 88.4 (d, $^2J_{C-F}$ = 17.7 Hz, CH, C-2′), 85.1 (s, CH, C-4′), 62.6 (s, $CH_2$, C-8′), 46.5 (d, $^2J_{C-F}$ = 18.3 Hz, CH, C-5′), 28.0 (d, $^2J_{C-F}$ = 22.5 Hz, $CH_2$, C-7′), 15.8 (d, $^3J_{C-F}$ = 17.9 Hz, $CH_2$, C-6′); $^{19}$F NMR (235 MHz, DMSO-$d_6$) $\delta$ −146.2 to −146.5 (m). HRMS (ESI+) calcd for $[C_{12}H_{14}FN_5O_2 + H]^+$ 280.1204, found 280.1203.

*(1′S,2′S,4′S,5′R)-9-(1′-Fluoro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-hypoxanthine (**53**).* To a solution of **45** (34 mg, 0.11 mmol) and MeONa (26 mg, 0.45 mmol) in dioxane (2 mL) were successively added 2-mercaptoethanol (32 $\mu$L, 0.45 mmol) and 2 drops of $H_2O$ at room temperature. The solution was heated at 110 °C for 15 h when the same initial amounts of MeONa, 2-mercaptoethanol, and $H_2O$ were added, and heating was continued for 4 days. Then, the solution was neutralized with glacial AcOH. The solvent was removed under vacuum, and the residue was purified by column chromatography (EtOAc−MeOH 9:1) to give **53** (22 mg, 0.08 mmol, 69% yield) as a white solid: mp 244−246 °C (MeOH); $[\alpha]_D$ −20.0 (*c* 0.30, DMSO); IR (ATR) 3319, 3061, 2853, 1691, 1169, 1033 cm$^{-1}$; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 12.40 (br s, 1H, N−H), 8.37 (s, 1H, H-8), 8.10 (s, 1H, H-2), 6.46 (d, $J_{2',F}$ = 16.1 Hz, 1H, H-2′), 5.05 (br s, 1H, OH), 4.28 (dd, *J* = 4.6 Hz, *J* = 4.4 Hz, 1H, H-4′), 3.52 (m, 2H, H-8′), 3.17 (m, 1H, H-5′), 2.16 (m, 2H, H-6′exo/7′exo), 1.56 (m, 1H, H-6′endo/7′endo); $^{13}$C NMR (90 MHz, DMSO-$d_6$) $\delta$ 156.5 (s, C, C-6), 147.7 (s, C, C-4), 146.2 (s, CH, C-2), 137.5 (s, CH, C-8), 124.2 (s, C, C-5), 102.1 (d, $^1J_{C-F}$ = 235.9 Hz, C, C-1′), 90.2 (d, $^2J_{C-F}$ = 40.8 Hz, CH, C-2′), 85.4 (d, $^3J_{C-F}$ = 1.4 Hz, CH, C-4′), 62.6 (s, $CH_2$, C-8′), 45.2 (d, $^2J_{C-F}$ = 18.2 Hz, CH, C-5′), 25.2 (d, $^2J_{C-F}$ = 22.8 Hz, $CH_2$, C-7′), 14.9 (d, $^3J_{C-F}$ = 16.1 Hz, $CH_2$, C-6′); $^{19}$F NMR (235 MHz, DMSO-$d_6$) $\delta$ −142.2 to −142.5 (m). HRMS (ESI+) calcd for $[C_{12}H_{13}FN_4O_3 + Na]^+$ 303.0864, found 303.0860.

*(1′S,2′R,4′S,5′R)-9-(1′-Fluoro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-hypoxanthine (**54**).* To a solution of **46** (15 mg, 0.05 mmol) and MeONa (10 mg, 0.20 mmol) in dioxane (3 mL) were successively added 2-mercaptoethanol (11 $\mu$L, 0.20 mmol) and 3 drops of $H_2O$ at room temperature. The solution was heated at 110 °C for 22 h and then, after being cooled to room temperature, was neutralized with glacial AcOH. The solvent was removed under vacuum, and the residue was purified by column chromatography (EtOAc−MeOH 10:1) to give **54** (12 mg, 0.04 mmol, 86% yield) as a white solid: mp 127−129 °C (MeOH); $[\alpha]_D$ +8.0 (*c* 0.50, MeOH); IR (ATR) 3338, 3048, 2868, 1698, 1207, 1027; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 12.30 (br s, 1H, N−H), 8.23 (d, $J_{8,F}$ = 2.4 Hz, 1H, H-8), 8.08 (s, 1H, H-2), 6.43 (d, $J_{2',F}$ = 11.4 Hz, 1H, H-2′), 5.10 (br s, 1H, OH), 4.14 (ddd, $J_{4',5'}$ = 6.6 Hz, $J_{4',8'}$ = 4.6 Hz, $J_{4',8'}$ = 4.2 Hz, 1H, H-4′), 3.59 (dd, $J_{gem}$ = 11.7 Hz, $J_{8',4'}$ = 4.2 Hz, 1H, H-8′), 3.52 (dd, $J_{gem}$ = 11.7 Hz, $J_{8',4'}$ = 4.6 Hz, 1H, H-8′), 3.23 (m, 1H, H-5′), 2.41 (m, 2H, H-7′exo/7′endo), 2.23 (m, 1H, H-6′exo), 1.63 (m, 1H, H-6′endo); $^{13}$C NMR (90 MHz, DMSO-$d_6$) $\delta$ 156.6 (s, C, C-6), 147.8 (s, C, C-4), 146.2 (s, CH, C-2), 138.6 (d, $^4J_{C-F}$ = 3.2 Hz, CH, C-8), 123.6 (s, C, C-5), 98.2 (d, $^1J_{C-F}$ = 247.7 Hz, C, C-1′), 88.6 (d, $^2J_{C-F}$ = 17.7 Hz, CH, C-2′), 85.3 (s, CH, C-4′), 62.5 (s, $CH_2$, C-8′), 46.4 (d, $^2J_{C-F}$ = 18.3 Hz, CH, C-5′), 28.1 (d, $^2J_{C-F}$ = 22.4 Hz, $CH_2$, C-7′), 15.7 (d, $^3J_{C-F}$ = 17.7 Hz, $CH_2$, C-6′); $^{19}$F NMR (235 MHz, DMSO-$d_6$) $\delta$ −140.4 to −140.6 (m). HRMS (ESI+) calcd for $[C_{12}H_{13}FN_4O_3 + Na]^+$ 303.0864, found 303.0856.

*(1′S,2′S,4′S,5′R)-6-Chloro-9-(1′-chloro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-purine (**47**).* To an ice-cooled solution of **41** (132 mg, 0.31 mmol) in THF (4 mL) was added a 1.0 M solution of TBAF in THF (460 $\mu$L, 0.46 mmol), and the resulting solution was stirred for 1 h at room temperature. After removal of the solvent, the residue was purified by column chromatography (EtOAc−hexane 3:1) to afford **47** (85 mg, 0.27 mmol, 88% yield) as a white solid: mp 127−129 °C (from $CHCl_3$); $[\alpha]_D$ +29.7 (*c* 0.74, $CHCl_3$); IR (ATR) 3380, 3124, 2946, 1593, 1562, 1199 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 8.75 (s, 1H, H-2), 8.45 (s, 1H, H-8), 6.66 (d, *J* = 0.6 Hz, 1H, H-2′), 4.43 (ddd, $J_{4',8'}$ = 6.5 Hz, $J_{4',8'}$ = 4.0 Hz, $J_{4',5'}$ = 1.0 Hz, 1H, H-4′), 3.86 (ddd, $J_{gem}$ = 11.9 Hz, $J_{8',OH}$ = 6.3 Hz, $J_{8',4'}$ = 4.0 Hz, 1H, H-8′), 3.79 (ddd, $J_{gem}$ = 11.9 Hz, $J_{8',4'}$ = 6.5 Hz, $J_{8',OH}$ = 4.5 Hz, 1H, H-8′), 3.21 (ddd, $J_{5',6'}$ = 8.2 Hz, $J_{5',6'}$ = 6.0 Hz, $J_{5',4'}$ = 1.0 Hz, 1H, H-5′), 2.91 (dd, $J_{OH,8'}$ = 6.3 Hz, $J_{OH,8'}$ = 4.5 Hz, 1H, OH), 2.53 (m, 1H, H-6′exo), 2.35 (m, 1H, H-7′exo), 2.04 (m, 1H, H-7′endo), 1.82 (m, 1H, H-6′endo); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 152.4 (CH, C-2), 151.3/151.2 (2C, C-4/C-6), 142.7 (CH, C-8), 131.7 (C, C-5), 93.4 (CH, C-2′), 86.4 (CH, C-4′), 70.2 (C, C-1′), 63.2 ($CH_2$, C-8′), 49.7 (CH, C-5′), 29.7 ($CH_2$, C-7′), 20.0 ($CH_2$, C-6′). HRMS (ESI+) calcd for $[C_{12}H_{12}Cl_2N_4O_2 + Na]^+$ 337.0230, found 337.0222.

*(1′S,2′S,4′S,5′R)-9-(1′-Chloro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-adenine (**51**).* A solution of **47** (25 mg, 0.08 mmol) in saturated $NH_3$/MeOH (4 mL) was heated at 90 °C in a sealed tube for 68 h. After cooling at room temperature, the solvent was removed under vacuum, and the resulting residue was purified by column chromatography ($CH_2Cl_2$−MeOH, 10:1) to afford **51** (21 mg, 0.07 mmol, 91% yield) as a white solid: mp 90−93 °C (from MeOH); $[\alpha]_D$ +26.7 (*c* 0.60, MeOH); IR (ATR) 3327, 3168, 2947, 2852, 1640, 1598, 1090, 1070 cm$^{-1}$; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 8.48 (s, 1H, H-8), 8.16 (s, 1H, H-2), 7.34 (br s, 2H, $NH_2$), 6.57 (s, 1H, H-2′), 5.09 (t, $J_{OH,8'}$

= 5.5 Hz, 1H, OH), 4.28 (t, $J$ = 5.1 Hz, 1H, H-4′), 3.55 (m, 2H, H-8′), 3.22 (dd, $J_{5',6'}$ = 9.2 Hz, $J_{5',6'}$ = 6.1 Hz, 1H, H-5′), 2.41 (m, 1H, H-6′exo), 2.25 (m, 1H, H-7′exo), 2.11 (m, 1H, H-7′endo), 1.90 (m, 1H, H-6′endo); $^{13}$C NMR (90 MHz, DMSO-$d_6$) $\delta$ 157.0 (C, C-6), 153.9 (CH, C-2), 150.2 (C, C-4), 139.3 (CH, C-8), 120.0 (C, C-5), 93.0 (CH, C-2′), 86.4 (CH, C-4′), 72.3 (C, C-1′), 63.0 ($CH_2$, C-8′), 50.2 (CH, C-5′), 30.5 ($CH_2$, C-7′), 20.3 ($CH_2$, C-6′). HRMS (ESI+) calcd for $[C_{12}H_{14}ClN_5O_2 + Na]^+$ 318.0728, found 318.0726.

*(1′S,2′R,4′S,5′R)-6-Chloro-9-(1′-chloro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-purine (**48**).* To an ice-cooled solution of **42** (40 mg, 0.09 mmol) in THF (3 mL) was added $Et_3N \cdot 3HF$ (44 $\mu$L, 0.27 mmol), and the resulting solution was stirred 20 h at room temperature. Evaporation of the solvent gave a residue which was purified by column chromatography (EtOAc−hexane 2:1) to afford **48** (28 mg, 0.09 mmol, 95% yield) as a colorless oil: $[\alpha]_D$ −23.6 ($c$ 0.55, $CHCl_3$); IR (ATR) 3345, 3110, 2945, 1590, 1561, 1336, 1206 cm$^{-1}$; $^1$H NMR (360 MHz, $CDCl_3$) $\delta$ 8.74 (s, 1H, H-2), 8.43 (s, 1H, H-8), 6.58 (s, 1H, H-2′), 4.36 (ddd, $J_{4',8'}$ = 4.5 Hz, $J_{4',8'}$ = 3.2 Hz, $J_{4',5'}$ = 3.2 Hz, 1H, H-4′), 3.97 (dd, $J_{gem}$ = 12.1 Hz, $J_{8',4'}$ = 3.1 Hz, 1H, H-8′), 3.81 (dd, $J_{gem}$ = 12.1 Hz, $J_{8',4'}$ = 4.5 Hz, 1H, H-8′), 3.39 (m, 1H, H-5′), 3.15 (br s, 1H, OH), 2.90 (m, 1H, H-7′endo), 2.65 (m, 2H, H-6′exo, H-7′exo), 1.99 (m, 1H, H-6′endo); $^{13}$C NMR (90 MHz, $CDCl_3$) $\delta$ 151.9 (CH, C-2), 151.3/151.2 (2C, C-4/C-6), 144.0 (CH, C-8), 131.8 (C, C-5), 92.8 (CH, C-2′), 86.9 (CH, C-4′), 72.0 (C, C-1′), 63.4 ($CH_2$, C-8′), 50.2 (CH, C-5′), 34.1 ($CH_2$, C-7′), 21.4 ($CH_2$, C-6′). HRMS (ESI+) calcd for $[C_{12}H_{12}Cl_2N_4O_2 + H]^+$ 315.0410, found 315.0405.

*(1′S,2′R,4′S,5′R)-9-(1′-Chloro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-adenine (**52**).* A solution of **48** (15 mg, 0.05 mmol) and saturated $NH_3$/MeOH (4 mL) was heated at 90 °C in a sealed tube for 70 h. After cooling at room temperature, the solvent was removed under vacuum, and the resulting residue was purified by column chromatography ($CH_2Cl_2$−MeOH, 10:1) to afford **52** (12 mg, 0.04 mmol, 92% yield) as a white solid: mp 233−235 °C (from MeOH); $[\alpha]_D$ −36.0 ($c$ 0.25, MeOH); IR (ATR) 3328, 3104, 2926, 1726, 1606, 1300, 1081, 1014 cm$^{-1}$; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 8.29 (s, 1H, H-8), 8.14 (s, 1H, H-2), 7.30 (br s, 2H, $NH_2$), 6.56 (s, 1H, H-2′), 5.13 (t, $J_{OH,8'}$ = 6.0 Hz, $J_{OH,8'}$ = 5.7 Hz, 1H, OH), 4.29 (ddd, $J$ = 4.4 Hz, $J$ = 3.6 Hz, $J$ = 3.3 Hz, 1H, H-4′), 3.60 (m, 2H, H-8′), 3.24 (m, 1H, H-5′), 2.86 (m, 1H, H-7′), 2.45 (m, 2H, H-6′exo, H-7′), 1.99 (m, 1H, H-6′endo); $^{13}$C NMR (90 MHz, DMSO-$d_6$) $\delta$ 156.9 (C, C-6), 153.7 (CH, C-2), 149.9 (C, C-4), 139.5 (CH, C-8), 119.4 (C, C-5), 91.6 (CH, C-2′), 86.6 (CH, C-4′), 73.5 (C, C-1′), 63.2 ($CH_2$, C-8′), 51.2 (CH, C-5′), 34.4 ($CH_2$, C-7′), 21.7 ($CH_2$, C-6′). HRMS (ESI+) calcd for $[C_{12}H_{14}ClN_5O_2 + H]^+$ 296.0909, found 296.0913.

*(1′S,2′S,4′S,5′R)-9-(1′-Chloro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-hypoxanthine (**55**).* To a solution of **47** (37 mg, 0.12 mmol) and MeONa (27 mg, 0.47 mmol) in dioxane (2 mL) were successively added 2-mercaptoethanol (33 $\mu$L, 0.47 mmol) and 2 drops of $H_2O$ at room temperature. The solution was heated at 110 °C for 17 h when the same amount of MeONa, 2-mercaptoethanol, and $H_2O$ was added, and heating was continued for 2 days. Then, the solution was neutralized with glacial AcOH. The solvent was removed under vacuum, and the residue was purified by column chromatography (EtOAc−MeOH 9:1) to afford **55** (26 mg, 0.09 mmol, 74% yield) as a white solid: mp 206−208 °C (MeOH); $[\alpha]_D$ +35.0 ($c$ 0.80, MeOH); IR (ATR) 3276, 3102, 3063, 2921, 2859, 1684, 1094 cm$^{-1}$; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 12.43 (br s, 1H, N−H), 8.44 (s, 1H, H-8), 8.08 (s, 1H, H-2), 6.54 (s, 1H, H-2′), 5.08 (br s, 1H, OH), 4.29 (t, $J$ = 4.8 Hz, 1H, H-4′), 3.54 (m, 2H, H-8′), 3.23 (dd, $J_{5',6'}$ = 8.9 Hz, $J_{5',6'}$ = 6.4 Hz, 1H, H-5′), 2.40 (m, 1H, H-6′exo), 2.25 (m, 1H, H-7′exo), 2.06 (m, 1H, H-7′endo), 1.88 (m, 1H, H-6′endo); $^{13}$C NMR (90 MHz, DMSO-$d_6$) $\delta$ 157.5 (C, C-6), 148.9 (C, C-4), 147.2 (CH, C-2), 138.8 (CH, C-8), 125.1 (C, C-5), 93.4 (CH, C-2′), 86.7 (CH, C-4′), 72.4 (C, C-1′), 63.1 ($CH_2$, C-8′), 50.3 (CH, C-5′), 30.5 ($CH_2$, C-7′), 20.3 ($CH_2$, C-6′). HRMS (ESI+) calcd for $[C_{12}H_{13}ClN_4O_3 + Na]^+$ 319.0568, found 319.0558.

*(1′S,2′R,4′S,5′R)-9-(1′-chloro-4′-hydroxymethyl-3′-oxabicyclo[3.2.0]hept-2-yl)-9H-hypoxanthine (**56**).* To a solution of **48** (10 mg, 0.03 mmol) and MeONa (7 mg, 0.12 mmol) in dioxane (2 mL) were successively added 2-mercaptoethanol (9 $\mu$L, 0.12 mmol) and 2 drops of $H_2O$ at room temperature. The solution was heated at 110 °C for 16 h and then, after being cooled to room temperature, was neutralized with glacial AcOH. The solvent was removed under vacuum, and the residue was purified by column chromatography (EtOAc−MeOH, 10:1) to give **56** (9 mg, 0.03 mmol, 96% yield) as a white solid: mp 130−133 °C (MeOH); $[\alpha]_D$ −18.0 ($c$ 0.50, MeOH); IR (ATR) 3345, 3050, 2869, 1684, 1210 cm$^{-1}$; $^1$H NMR (360 MHz, DMSO-$d_6$) $\delta$ 12.40 (br s, 1H, N−H), 8.25 (s, 1H, H-8), 8.07 (s, 1H, H-2), 6.53 (s, 1H, H-2′), 5.08 (br s, 1H, OH), 4.21 (ddd, $J_{4',8'}$ = 5.2 Hz, $J_{4',8'}$ = 4.7 Hz, $J_{4',5'}$ = 3.6 Hz, 1H, H-4′), 3.61 (dd, $J_{gem}$ = 11.9 Hz, $J_{8',4'}$ = 4.7 Hz, 1H, H-8′), 3.56 (dd, $J_{gem}$ = 11.9 Hz, $J_{8',4'}$ = 5.2 Hz, 1H, H-8′), 3.23 (m, 1H, H-5′), 2.82 (m, 1H, H-7′exo), 2.45 (m, 2H, H-6′exo, H-7′exo), 1.98 (m, 1H, H-6′endo); $^{13}$C NMR (62.5 MHz, DMSO-$d_6$) $\delta$ 156.5 (C, C-6), 147.6 (C, C-4), 146.1 (CH, C-2), 137.9 (CH, C-8), 123.8 (C, C-5), 90.8 (CH, C-2′), 85.9 (CH, C-4′), 72.5 (C, C-1′), 62.1 ($CH_2$, C-8′), 50.1 (CH, C-5′), 33.4 ($CH_2$, C-7′), 20.5 ($CH_2$, C-6′). HRMS (ESI+) calcd for $[C_{12}H_{13}ClN_4O_3 + Na]^+$ 319.0568, found 319.0551.

## ■ ASSOCIATED CONTENT

**Supporting Information.** $^1$H and $^{13}$C NMR spectra of all new compounds and 2D NMR spectra for compounds **32**−**33** and **49**−**56**. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Author**
*E-mail: ramon.alibes@uab.cat.

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## ■ DEDICATION

Dedicated to the memory of Prof. Rafael Suau.

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