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Synthesis of Novel Nucleosides with a Fused Cyclopropane Ring Substituted by a Hydroxymethyl Group

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Abstract—The two diastereomers of a 3-oxabicyclo[3.1.0]hexan-2-ol **21a**–**b** with the cyclopropane ring substituted by a hydroxymethyl group were synthesized from both products **17a** and **18a** obtained from the bromohydroxylation of epoxide **16a** derived from 3-oxabicyclo[3.2.0]hept-6-en-2-one **15**. This preparation involved two stereospecific C_4–C_3 ring contractions leading to *cis*,*cis*-trisubstituted cyclopropane compounds **18a** and **12**. The hydroxylactols **21a**–**b** thus obtained were diacetylated and the single product **22** was subjected to substitution at the anomeric position by protected or free bases, providing, in each case, only one of the possible products. Deprotection with ammonia yielded new bicyclic nucleosides **11a**–**d**. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

In recent years, numerous nucleosides with modifications of the sugar unit have been described with the hope of obtaining new antiviral and anticancer agents.[1] In this area, several works were devoted to the preparation of bicyclic compounds,[2] including cyclopropano homologs[3] **2**, **3**, **4** of 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T) **1**, which is one of the nucleosides approved by the F.D.A. for treatment of HIV infection. In these molecules, the double bond was replaced by a cyclopropane ring via cyclopropanation,[3a] homologous Ferrier reaction,[3b,c] 1,3-dipolar cycloaddition[3d]

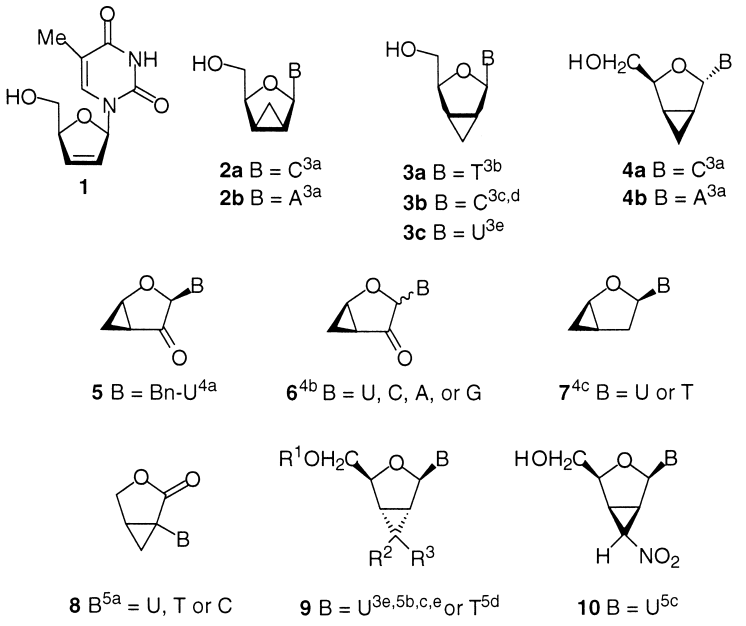

Figure 1.

Keywords: ring contraction; stereoselection; substitution; bicyclic nucleosides.

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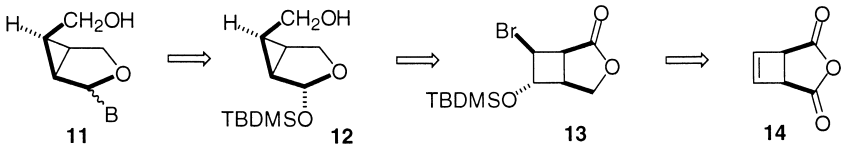


Scheme 1.

or Michael addition.[3e] These analogs were expected to be more stable than **1** to glycosyl cleavage because the intermediate carbonium ion should be less stabilized.[3b] As such a cleavage leads to inactivation, this modification should be interesting if these compounds keep the biological properties. Unfortunately, **3b** had only a weak anti-HIV activity[3c,d] and **3a** was inactive against several viruses.[3b] Other bicyclonucleosides disubstituted[4] on the cyclopropane moiety **5–7**, and tri- or tetrasubstituted[3e,5] **8–10** have also been prepared (Fig. 1) for potential applications in the field of therapeutics based on nucleosides or oligonucleotides.

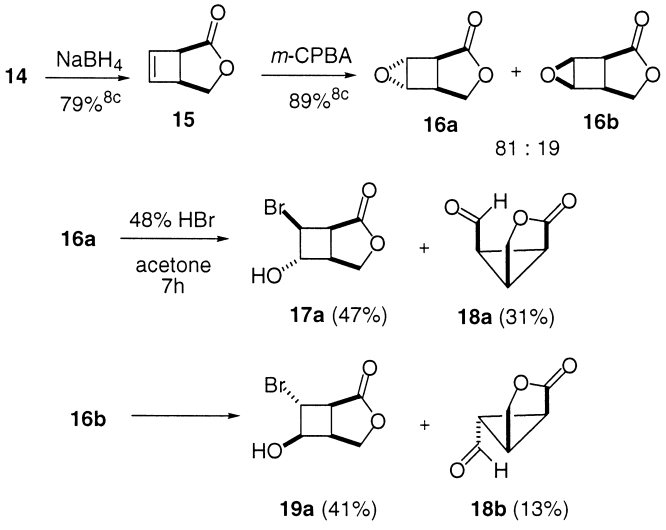
In the course of our research program concerning the synthesis of new carbocyclic nucleosides, we obtained the lactone **13**,[6] in several steps, starting from cyclobutene anhydride **14**.[7] We intended to use it in the preparation of the corresponding non-halogenated diol by concomitant reduction of the lactone moiety and of the carbon–halide bond. However, reaction with $LiAlH_4$ proceeded without removal of the halide and a following reduction of this halogenated diol in more drastic conditions ($LiEt_3BH$) produced a certain amount of the unexpected ring contraction product **12**.[6] Nevertheless, we thought that this compound **12**, with a *cis*,*cis*-relationship between substituents of the cyclopropane moiety, which would probably not be easily available by another way, might be interesting for synthetic applications. We thus envisaged improving the experimental conditions for obtaining **12** and then using it for the preparation of new fused cyclopropane-containing nucleosides **11** by substitution at the anomeric position (Scheme 1).

Results and Discussion

In previous works, anhydride **14**[7] was reduced to the lactone **15**[8] that was epoxidized leading to **16a**, predominantly.[8c] Treatment of epoxide **16a** with aqueous hydrobromic acid afforded a mixture of bromohydrin **17a** and compound **18a**, the configuration of which was not assigned.[8c] We have now improved both their yields and this aldehyde **18a** has been identified as the *cis*,*cis*-isomer (see below). At this point, to gain insight into the mechanism of the ring contraction that occurred in acidic medium, some additional experiments were carried out. We thus subjected epoxide **16b** to the same experimental conditions and also obtained a mixture of two compounds, bromohydrin **19a** and aldehyde **18b** (Scheme 2).

Identification of **19a** began by assignment of H-5 owing to its coupling together with H-1, H-4, H-6 and even with H-7 (0.8 Hz). Successive spin decoupling experiments starting from H-5 led to assignments of H-1, H-4, H-6 and H-7. Configurations were then deduced from NOE experiments (Fig. 2). The structures of aldehydes **18a** and **18b** were also based on NOE experiments and on the fact that the *cis* vicinal coupling constants are always larger than the *trans* ones for two stereomer cyclopropanes.[9] Furthermore, the relative instability of **18a**, which provided **20** slowly on standing, also confirmed the *cis*,*cis*-stereochemistry of **18a** (Scheme 3).

Ring contractions from epoxides and bromohydrins have already been reported by numerous research groups and



Scheme 2.

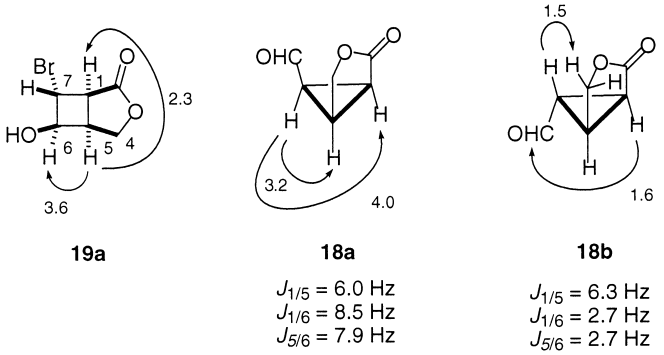
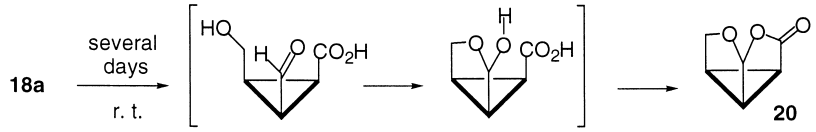
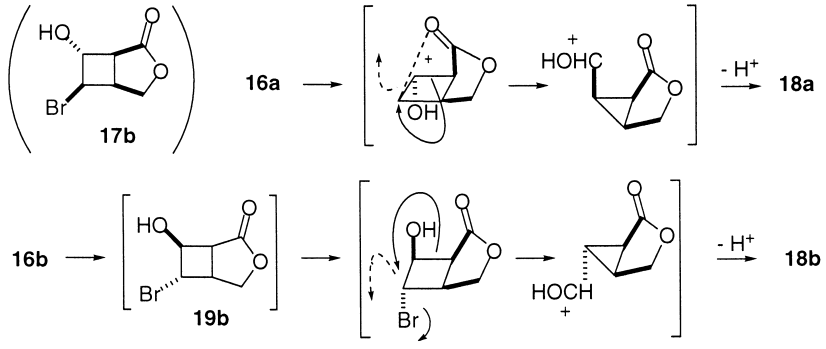


Figure 2. NOE enhancements (%) and coupling constants.

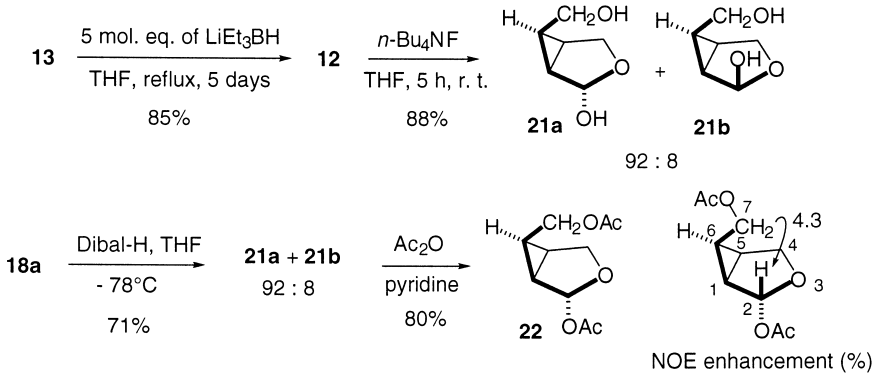


Scheme 3.

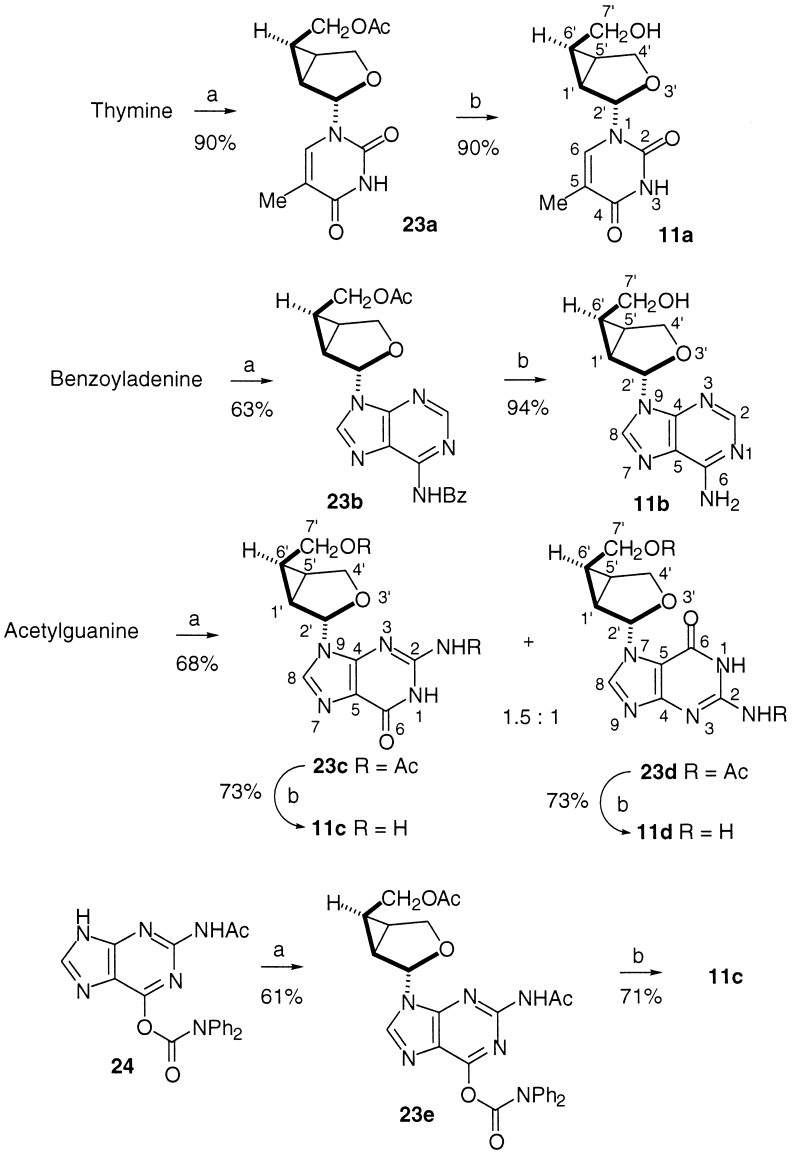
have led to several synthetic applications.[6,10] In the case of the formation of **18a** and **18b**, the interesting point is obtaining only one isomer in each reaction. When starting from **16a**, bromohydrin **17a** was formed and appeared relatively stable in the reaction mixture. As the other isomer **17b** was not observed, one hypothesis for the formation of **18a** would be via the ring contraction from this bromohydrin. However, it is more likely that **17b** is not obtained at all but that **18a** is derived directly from an intermediate carbonium ion stabilized by anchimeric assistance of the vicinal carbonyl group (Scheme 4). Breaking the C–C bond close to the hydroxyl group and attacking the corresponding electron doublet from the other side could thus provide the rearranged carbonium ion with the *cis*,*cis*-structure. In contrast, for the reaction from **16b**, protonation leads to an intermediate with the hydroxyl group on the same side as the carbonyl



Scheme 4.



Scheme 5.



Scheme 6. (a) 1: BSA, MeCN; 2: TMSOTf; 3: **22**, 2 h; 4: $NaHCO_3$; (b) NH_3, MeOH, 2–7 days.

group and such an anchimeric stabilization should be more difficult. Therefore, in this case, the ring contraction probably works via bromohydrin **19b**, which may explain obtaining the *trans* product.[10c] Finally, in both cases, bromohydrins **17a** or **19a**, with the hydroxyl group linked to C-6, could be isolated, whereas the 7-hydroxy intermediates yielded the cyclopropane compounds **18a** and **18b**.

Subsequently, we tried to optimize the synthesis of compound **12** with respect to our previous report.[6] After protection of bromohydrin **17a** with a silyl group to afford the lactone **13**,[6] we were pleased to observe that **12** could be directly prepared from **13** in one step instead of two in the early experiment. As a matter of fact, when **13** was reduced by 5 molar equivalents of $LiEt_3BH$ in THF, an 85% isolated yield of **12** was obtained (Scheme 5). The subsequent desilylation afforded the lactol **21** in a good yield as a mixture of both epimers in a 92:8 ratio. To avoid the protection–deprotection sequence, we also tried to subject **17a** to the same experimental conditions but we only obtained degradation products. Protection of the hydroxyl group then appeared as necessary. On the other hand, attempts of ring contraction of **17a** to **18a**, in basic medium and in several experimental conditions,[10] led either to recovery of the starting material or to degradation products.

These improvements to prepare **12**, **17a** and **18a** were important on the synthetic point of view, especially as we envisaged using not only **12**, derived from **17a**, but also **18a**, to produce compound **21**, the key intermediate of this work. Eventually reduction of **18a** by Dibal-H[11] afforded the lactol **21** in a satisfying yield (71%). Then acetylation led to the crude diacetate **22** as a single diastereomer. Purification by flash chromatography provided **22** in an 80% isolated yield

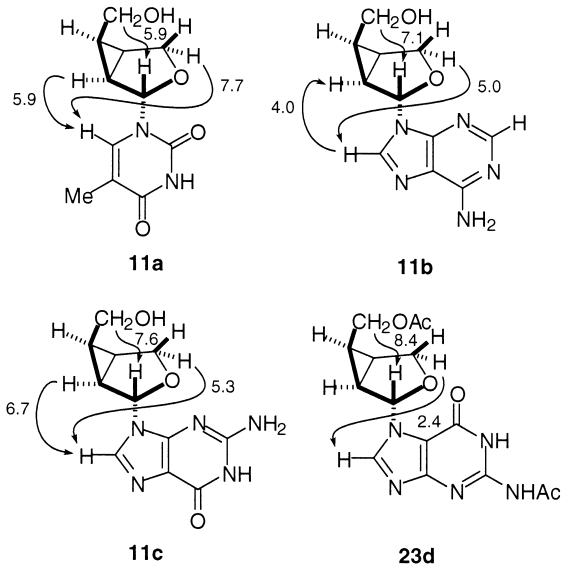


Figure 3. NOE enhancements (%).

together with a certain amount of the hydrolysis product at the anomeric position (10%, see the Experimental section). Configuration of the anomeric carbon was deduced from the 4.3% NOE enhancement of H-2 upon saturation of H-7. Compound **22** was thus available in satisfying overall yield (43% from **16a** when using **17a** and **18a**). This good result encouraged us to carry on our project towards the synthesis of bicyclic nucleosides.

When diacetate **22** was subjected to the one-pot substitution by thymine in Vorbrüggen et al. conditions,[12] modified by Dudycz et al.[13] (BSA, TMSOTf, MeCN), the expected product **23a** was obtained in excellent yield (Scheme 6). Condensation also worked with protected purine bases but in lower yield (63–68%). All attempts to increase the sugar-base coupling yield (amount of catalyst, of silylating agent, temperature, solvent composition…) have been unsuccessful

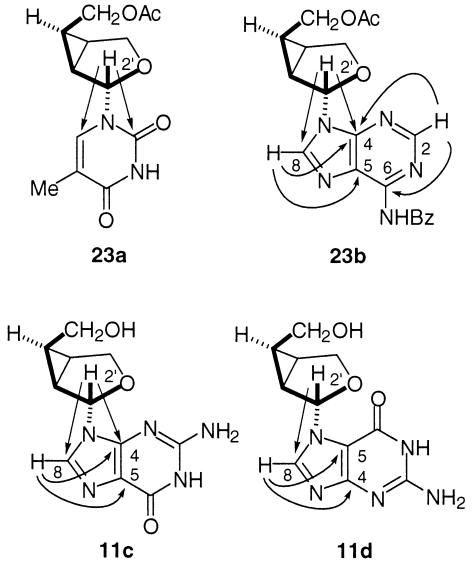


Figure 4. Relevant HMBC correlations.

and predominantly led to byproducts. However, regioselectivity was excellent from benzoyladenine, which exclusively led to the N-9 isomer **23b**. On the other hand, reaction with acetyl guanine gave a 1.5:1 mixture of the N-9/N-7 products, **23c** and **23d**, respectively, which were fortunately separable by column chromatography. As observed by several groups,[14] the use of disubstituted guanine **24** is necessary to overcome this problem and to get exclusively the N-9 derivative. In a last step, bicyclic nucleosides **11** were obtained after deprotection with a solution of ammonia in methanol.[15]

Stereochemical assignments were deduced from NOE experiments for **11a**, **11b**, **11c** and **23d** (Fig. 3). In each case, significant enhancement of signal for the anomeric proton H-2′ upon saturation of H-7′ (5.9–8.4%) showed that the nucleobases were fixed at the opposite side from the acetoxymethyl or hydroxymethyl group. Obtaining only one anomer may be due to the steric hindrance of the acetoxymethyl group.

Regiochemistries were elucidated by HMBC experiments (Fig. 4). In the case of **23b**, one quaternary carbon was correlated with H-2 and H-8, another one with H-8 and the third one with H-2. As C-5 is always at a higher field than C-4 and C-6 in adenine derivatives, H-2 and H-8 were thus distinguished. A $^{1}J^{13}C/^{1}H$ correlation then led to assignments of C-8 and C-2. Finally, the long range correlations between H-2′ and C-8 and C-4 proved the N-9 regiochemistry. In the case of **11c** and **11d**, H-8 was correlated only with C-4 and C-5 and as C-5 is at a higher field than C-4, they were both assigned. The long range correlations between H-2′ and C-8 and C-4 proved the N-9 regiochemistry for **11c**. For the nucleoside **11d**, correlation between H-2′ and C-5 could not been observed, but as **11c** had been undoubtedly identified, the H-2′/C-8 correlation proved the N-7 regiochemistry. Moreover, obtaining **11c** from **23e** was in full agreement with the previous results.

In conclusion, we pointed out that diacetate **22** was efficiently synthesized from the easily available epoxide **16a**, and we also proposed interpretations of our results of ring contractions. New bicyclic nucleosides **11a–d** were afterwards obtained from **22** by substitution at the anomeric position followed by deprotection. Biological tests showed that these compounds did not have antitumor properties. Their evaluations as anti-HIV agents are in progress. One of the interests of this strategy is the possibility of obtaining bicyclic compounds with a fused functionalized cyclopropane. However, coupling of bases exclusively led to products with an α-type configuration at the anomeric position. The use of this new route to prepare compounds with hydroxymethyl substituents linked to the five membered ring, which should have a better chance of having biological properties, is in due course.

Experimental

General

All the moisture-sensitive reactions were carried out in

oven-dried glassware (110°C) and under nitrogen atmosphere. Commercially available reagents and solvents were purified and dried, when necessary, by standard methods just prior to use. IR spectra were scanned on a FT infrared spectrophotometer. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS which was used as an internal reference. Multiplicities in the ^{13}C spectra were determined by DEPT experiments, and numerous assignments were obtained by ^{13}C/^{1}H HETCOR and HMBC experiments. Ratios in mixtures of epimers were calculated from ^{1}H NMR. Elemental analyses were obtained from the Service de Microanalyse, CNRS ICSN, Gif-sur-Yvette. High-resolution mass measurements were performed at the CRMPO, Rennes.

(1*R,5*S**,6*S**,7*S**)-7-Bromo-6-hydroxy-3-oxabicyclo[3.2.0]-heptan-2-one (17a) and (1*S**,5*S**,6*R**)-6-carbaldehyde-3-oxabicyclo[3.1.0]hexan-2-one (18a) and compound 20.** To an ice-cold solution of epoxide **16a**[8c] (2.07 g, 16.41 mmol) in acetone (130 mL) was added dropwise HBr (48% aqueous solution, 5.60 mL, 49.50 mmol). The reaction mixture was stirred for 7 h at room temperature and then was neutralized with an aqueous saturated solution of $NaHCO_3$ (40 mL). Acetone was removed in vacuo and the aqueous layer was extracted with EtOAc (6×40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (silica gel, CH_2Cl_2/Et_2O: 1/0→7/3) afforded compound **18a** (0.65 g, 5.15 mmol, 31%) as colorless crystals and then compound **17a** (1.60 g, 7.73 mmol, 47%) as white crystals.

*Compound **17a***. see Ref. 8c.

*Compound **18a***. mp 55–56°C; IR (KBr, cm^{-1}) 1762, 1698, 1691, 1168; ^{1}H NMR ($CDCl_3$) δ 9.47 (d, 1H, CHO, J=5.2 Hz), 4.61 (dd, 1H, H-4, J=10.5, 5.0 Hz), 4.51 (ddd, 1H, H-4′, J=10.5, 0.8, 0.8 Hz), 2.84 (m, 1H, H-5), 2.70 (ddd, 1H, H-1, J=8.5, 6.0, 0.8 Hz), 2.37 (ddd, 1H, H-6, J=8.5, 7.9, 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 196.4 (*C*HO), 172.2 (*C*=O), 66.7 (CH_2), 30.6 (*C*H), 27.3 (*C*H), 25.6 (*C*H); Anal. Calcd for $C_6H_6O_3$ (MW: 126.11): C, 57.14; H, 4.79. Found: C, 57.04; H, 4.81.

*Compound **20***. **18a** gave polycyclic compound **20** as a colorless oil, when it was left at room temperature for several days: IR (neat, cm^{-1}) 1764, 1191, 929; ^{1}H NMR ($CDCl_3$) δ 6.06 (d, 1H, J=3.3 Hz), 4.39 (dd, 1H, J=10.0, 5.2 Hz), 4.07 (dd, 1H, J=10.0, 1.4 Hz), 3.46 (ddd, 1H, J=7.3, 5.6, 3.3 Hz), 2.50 (m, 1H), 2.35 (dd, 1H, J=7.9, 5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 173.6 (*C*=O), 105.4 (*C*H), 68.7 (CH_2), 36.2 (*C*H), 30.4 (*C*H), 27.8 (*C*H); HRMS Calcd for $C_6H_6O_3$: $(M+H)^+$ 127.0395. Found: 127.0394.

(1*S,5*S**,6*S**)-6-Carbaldehyde-3-oxabicyclo[3.1.0]hexan-2-one (18b) and (1*R**,5*S**,6*R**,7*R**)-7-bromo-6-hydroxy-3-oxabicyclo[3.2.0]heptan-2-one (19a).** Following the same procedure as for the preparation of **17a** and **18a**, epoxide **16b** (0.40 g, 3.17 mmol) gave, after chromatography (silica gel, CH_2Cl_2/Et_2O: 1/0→4/1), compound **18b** (50 mg, 0.40 mmol, 13%) as a colorless oil and compound **19a** (268 mg, 1.29 mmol, 41%) as white crystals.

*Compound **18b***. IR (neat, cm^{-1}) 1768, 1712, 1172; ^{1}H NMR ($CDCl_3$) δ 9.62 (d, 1H, CHO, J=2.7 Hz), 4.48 (dd, 1H, H-4, J=10.1, 4.5 Hz), 4.36 (dd, 1H, H-4′, J=10.1, 0.6 Hz), 2.78 (ddd, 1H, H-5, J=6.3, 4.5, 2.7 Hz), 2.70 (ddd, 1H, H-1, J=6.3, 2.7, 0.6 Hz), 2.33 (ddd, 1H, H-6, J=2.7, 2.7, 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 195.4 (*C*HO), 173.0 (*C*=O), 68.9 (CH_2), 32.4 (*C*H), 26.3 (*C*H), 25.9 (*C*H); HRMS Calcd for $C_6H_6O_3$: 126.0317. Found: 126.0314.

*Compound **19a***. mp 94–95°C (Et_2O); IR (KBr, cm^{-1}) 3400, 1743, 1192; ^{1}H NMR (acetone-d_6) δ 5.52 (br s, 1H, OH), 4.74 (dd, 1H, H-4, J=9.8, 4.6 Hz), 4.63 (ddd, 1H, H-6, J=8.0, 5.8, 0.7 Hz), 4.41 (dd, 1H, H-4′, J=9.8, 9.8 Hz), 4.36 (ddd, 1H, H-7, J=5.8, 5.8, 0.8 Hz), 3.63 (m, 1H, H-5), 3.04 (ddd, 1H, H-1, J=8.4, 5.8, 0.7 Hz); ^{13}C NMR (acetone-d_6) δ 176.1 (*C*=O), 74.1 (*C*H), 66.2 (CH_2), 49.7 (*C*H), 43.0 (*C*H), 39.8 (*C*H); Anal. Calcd for $C_6H_7O_3Br$ (MW: 207.02): C, 34.81; H, 3.41; Br, 38.60. Found: C, 34.74; H, 3.41; Br, 38.52.

(1*S,2*R**,5*R**,6*S**)-6-Hydroxymethyl-2-[(*tert*-butyldimethylsilyl)oxy]-3-oxabicyclo[3.1.0]hexane (12).** A solution of **13** (2.73 g, 8.50 mmol) in anhydrous THF (84 mL) was added dropwise to a solution of $LiEt_3BH$ (42.50 mL of a 1 M solution in THF, 42.50 mmol). The resulting mixture was stirred for 5 days at reflux. After cooling to 0°C, KOH 2 M (4.25 mL, 8.50 mmol) then H_2O (4 mL) were added and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (500 mL), washed (brine, 140 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (silica gel, CH_2Cl_2/EtOAc: 1/0→4/1) afforded **12** (1.76 g, 7.22 mmol, 85%) as a colorless oil: IR (neat, cm^{-1}) 3350, 2929, 2856, 1251, 1083, 1039, 836; ^{1}H NMR ($CDCl_3$) δ 5.32 (s, 1H, H-2), 4.14 (dd, 1H, H-4, J=8.7, 3.7 Hz), 3.82 (d, 1H, H-4′, J=8.7 Hz), 3.74 (d, 2H, CH_2OH, J=7.5 Hz), 1.86 (m, 1H, H-5), 1.80 (dd, 1H, H-1, J=8.1, 7.0 Hz), 1.34 (br s, 1H, OH), 1.22 (m, 1H, H-6), 0.90 (s, 9H, (CH_3)$_3$C), 0.12 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{13}C NMR ($CDCl_3$) δ 97.8 (C2), 66.4 (C4), 57.4 (*C*H_2OH), 28.5 (C1), 25.7 ((*C*H_3)$_3$C), 21.2 (C6), 19.9 (C5), 17.9 ((CH$_3$)$_3$*C*), −4.3 (*C*H_3Si), −5.0 (*C*H_3Si); Anal. Calcd for $C_{12}H_{24}O_3Si$ (MW: 244.41): C, 58.97; H, 9.90; Si, 11.49. Found: C, 58.62; H, 9.91; Si, 11.74; HRMS Calcd for $C_{12}H_{24}O_3Si$: $(M-H)^+$ 243.1416. Found: 243.1422.

(1*S,2*S**,5*R**,6*S**)-6-Hydroxymethyl-3-oxabicyclo[3.1.0]-hexan-2-ol (21a) and (1*S**,2*R**,5*R**,6*S**)-6-hydroxymethyl-3-oxabicyclo[3.1.0]hexan-2-ol (21b).** *Procedure A:* A 1 M solution of *n*-Bu_4NF in THF (16.00 mL, 16.00 mmol) was added to a solution of compound **12** (1.37 g, 5.60 mmol) in anhydrous THF (24 mL). The reaction mixture was stirred at room temperature for 5 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (silica gel, EtOAc/MeOH: 1/0→98/2) to afford a mixture of both epimers **21a** and **21b** in a 92:8 ratio (641 mg, 4.93 mmol, 88%) as a colorless oil: IR (neat, cm^{-1}) 3382, 2886, 1022; ^{1}H NMR major isomer **21a** (acetone-d_6) δ 5.22 (d, 1H, H-2, J=5.7 Hz), 5.07 (d, 1H, OH, J=5.7 Hz), 4.04 (dd, 1H,

H-4, J=8.4, 3.8 Hz), 3.73 (d, 1H, H-4′, J=8.4 Hz), 3.59 (m, 2H, CH_2OH), 3.41 (t, 1H, CH$_2$OH, J=5.5 Hz), 1.77 (m, 1H, H-5), 1.69 (dd, 1H, H-1, J=8.3, 6.8 Hz), 1.17 (m, 1H, H-6); ^{1}H NMR minor isomer **21b** (acetone-d_6) 5.80 (d, 1H, OH, J=9.8 Hz), 5.49 (dd, 1H, H-2, J=9.8, 2.8 Hz), 4.37 (dd, 1H, CH$_2$OH, J=5.3, 4.8 Hz), 4.00 (ddd, 1H, CH_2OH, J=11.3, 7.4, 4.8 Hz), 3.89 (dd, 1H, H-4, J=9.1, 3.3 Hz), 3.86 (d, 1H, H-4′, J=9.1 Hz), 3.68 (ddd, 1H, CH_2OH, J=11.3, 10.1, 5.3 Hz), 1.80 (ddd, 1H, H-1, J=8.1, 7.2, 2.8 Hz), 1.26 (m, 1H, H-6) (H-5 hidden by a signal of the major isomer); ^{13}C NMR major isomer **21a** (acetone-d_6) δ 97.9 (*C*H), 66.4 (*C*H$_2$), 56.9 (*C*H$_2$), 28.1 (*C*H), 22.4 (*C*H), 20.5 (*C*H); ^{13}C NMR minor isomer **21b** (acetone-d_6) δ 100.6 (*C*H), 66.0 (*C*H$_2$), 57.1 (*C*H$_2$), 26.2 (*C*H), 22.3 (*C*H), 21.4 (*C*H); Anal. Calcd for $C_6H_{10}O_3\cdot 0.2H_2O$ (MW: 133.75): C, 53.88; H, 7.84. Found: C, 53.92; H, 7.84.

Procedure B: To a cold solution (−78°C) of **18a** (314 mg, 2.49 mmol) in anhydrous THF (5.4 mL) was added a 1 M solution of Dibal-H in THF (7.60 mL, 7.60 mmol) over a period of 1 h and in a temperature below −68°C. After 2 h stirring at −78°C, the reaction mixture was quenched with MeOH (1.4 mL) and allowed to warm to room temperature. EtOAc (14 mL) and saturated $NaHCO_3$ solution (1.4 mL) were added and the mixture was stirred for 2 h. Powdered Na_2SO_4 (3.2 g) was then added and stirring was continued overnight. The precipitate was removed by filtration and washed with EtOAc. The solvent was evaporated in vacuo and the residue thus obtained was purified by column chromatography (silica gel, EtOAc/CH_2Cl_2: 1/1→2/1+5% MeOH) to yield a mixture of both epimers **21a** and **21b** in a 92:8 ratio (232 mg, 1.78 mmol, 71%) as a colorless oil.

(1*R,2*R**,5*R**,6*S**)-2-Acetyloxy-6-acetyloxymethyl-3-oxabicyclo[3.1.0]hexane (22).** Acetic anhydride (1.70 mL, 18.10 mmol) was added dropwise to an ice-cold stirred solution of **21a**+**21b** (460 mg, 3.53 mmol) in pyridine (5.0 mL). The reaction mixture was stirred for 30 min at 0°C and then at room temperature overnight. After cooling to 0°C, MeOH (2.0 mL) was added. The mixture was then allowed to warm to room temperature and concentrated to dryness. The crude product was purified by flash chromatography (silica gel, cyclohexane/EtOAc: 9/1→2/1) to yield diacetate **22** (604 mg, 2.82 mmol, 80%) as a colorless oil and lactol obtained from partial hydrolysis of **22** on silica gel (61 mg, 0.35 mmol, 10%, 97:3 ratio of epimers) as a colorless oil.

Compound 22. IR (neat, cm^{-1}) 1741, 1236; ^{1}H NMR ($CDCl_3$) δ 6.18 (s, 1H, H-2), 4.23 (dd, 1H, CH_2OAc, J=11.7, 7.7 Hz), 4.20 (dd, 1H, H-4, J=9.0, 3.4 Hz), 4.13 (dd, 1H, CH_2OAc, J=11.7, 7.9 Hz), 3.97 (d, 1H, H-4′, J=9.0 Hz), 2.08 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 1.99–1.90 (m, 2H, H-1 and H-5), 1.41 (m, 1H, H-6); ^{13}C NMR ($CDCl_3$) δ 170.9 (*C*=O), 170.1 (*C*=O), 97.4 (*C*H), 67.9 (*C*H$_2$), 59.3 (*C*H$_2$), 25.8 (*C*H), 21.2 (*C*H$_3$), 20.9 (*C*H$_3$), 19.6 (*C*H), 17.7 (*C*H); Anal. Calcd for $C_{10}H_{14}O_5$ (MW: 214.22): C, 56.07; H, 6.59. Found: C, 55.99; H, 6.69.

Hydrolysis product. IR (neat, cm^{-1}) 3425, 1732, 1240; ^{1}H NMR major isomer ($CDCl_3$) δ 5.35 (d, 1H, H-2, J=4.3 Hz), 4.25–4.12 (m, 3H, CH_2OAc and H-4), 3.89 (d, 1H, H-4′, J=8.9 Hz), 2.88 (d, 1H, OH, J=4.3 Hz), 2.07 (s, 3H, CH_3), 1.95–1.86 (m, 2H, H-1 and H-5), 1.34 (m, 1H, H-6); ^{1}H NMR minor isomer ($CDCl_3$) δ 5.60 (dd, 1H, H-2, J=10.5, 2.6 Hz), 4.60 (dd, 1H, CH_2OAc, J=12.0, 6.0 Hz), 4.45 (dd, 1H, CH_2OAc, J=12.0, 9.2 Hz), 4.36 (d, 1H, OH, J=10.5 Hz), 3.99 (dd, 1H, H-4, J=9.5, 3.2 Hz), 3.96 (d, 1H, H-4′, J=9.5 Hz), 2.10 (s, 3H, CH_3) 1.86–1.79 (m, 2H, H-1 and H-5) (H-6 hidden by a signal of the major isomer); ^{13}C NMR major isomer ($CDCl_3$) δ 171.1 (*C*=O), 97.4 (*C*H), 66.4 (*C*H$_2$), 59.8 (*C*H$_2$), 27.2 (*C*H), 21.0 (*C*H$_3$), 19.8 (*C*H), 17.8 (*C*H); HRMS Calcd for $C_8H_{12}O_4$: 172.0735. Found: 172.0737.

(1′*R,2′*S**,5′*R**,6′*S**)-1-(6′-Acetyloxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)thymine (23a).** BSA (306 μL, 1.20 mmol) was added to a suspension of thymine (53 mg, 0.42 mmol) in anhydrous MeCN (3 mL), and stirring was continued for 15 min at room temperature until a clear solution was obtained. Diacetate **22** (86 mg, 0.40 mmol) in anhydrous MeCN (2 mL) and TMSOTf (80 μL, 0.41 mmol) were successively added at 0°C. The reaction mixture was stirred at room temperature for 2 h. CH_2Cl_2 (2 mL) was added and the reaction mixture was quenched with aqueous saturated $NaHCO_3$ (4.0 mL). Solvents were removed in vacuo, the residue was dissolved in EtOAc (25 mL) and the solution was washed with water (20 mL), dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc: 1/0→2/1) to give **23a** (101 mg, 0.36 mmol, 90%) as a white solid: mp 211–212°C; IR (KBr, cm^{-1}) 3035, 1724, 1704, 1662, 1249; ^{1}H NMR ($CDCl_3$) δ 8.95 (br s, 1H, NH), 7.11 (d, 1H, H6, J=0.9 Hz), 6.08 (s, 1H, H-2′), 4.28 (dd, 1H, H-4′, J=9.3, 4.0 Hz), 4.26 (dd, 1H, CH_2OAc, J=11.9, 7.7 Hz), 4.20 (dd, 1H, CH_2OAc, J=11.9, 7.7 Hz), 4.05 (d, 1H, H-4″, J=9.3 Hz), 2.20 (m, 1H, H-5′), 2.10 (s, 3H, CH_3CO$_2$), 2.03 (dd, 1H, H-1′, J=8.4, 6.6 Hz), 1.95 (d, 3H, CH_3 base, J=0.9 Hz), 1.57 (m, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 171.0 (CH_3CO_2), 163.8 (C-4), 150.5 (C-2), 135.4 (C-6), 111.1 (C-5), 85.3 (C-2′), 68.9 (C-4′), 59.0 (CH_2OAc), 26.4 (C-1′), 21.8 (C-5′), 20.9 (CH_3CO$_2$), 18.4 (C-6′), 12.7 (CH_3 base); Anal. Calcd for $C_{13}H_{16}N_2O_5$ (MW: 280.28): C, 55.71; H, 5.75; N, 9.99. Found: C, 55.89; H, 5.76; N, 9.97; HRMS Calcd for $C_{13}H_{16}N_2O_5$: 280.1059. Found: 280.1057.

(1′*R,2′*S**,5′*R**,6′*S**)-9-(6′-Acetyloxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)-6-*N*-benzoyladenine (23b).** Reaction from BSA (450 μL, 1.76 mmol), 6-*N*-benzoyladenine (200 mg, 0.84 mmol), diacetate **22** (123 mg, 0.57 mmol) and TMSOTf (145 μL, 0.75 mmol), in the same experimental conditions as for **23a**, led to **23b** as a white solid (142 mg, 0.36 mmol, 63%) after column chromatography (silica gel, CH_2Cl_2/MeOH: 98/2): mp 173–174°C; IR (KBr, cm^{-1}) 1726, 1705, 1514, 1248; ^{1}H NMR ($CDCl_3$) δ 9.06 (br s, 1H, NH), 8.81 (s, 1H, H-2), 8.14 (s, 1H, H-8), 8.03 (d, 2H, arom, J=7.3 Hz), 7.61 (m, 1H, arom), 7.53 (m, 2H, arom), 6.37 (s, 1H, H-2′), 4.39 (dd, 1H, CH_2OAc, J=11.8, 7.3 Hz), 4.33 (dd, 1H, H-4′, J=9.3, 3.6 Hz), 4.31 (dd, 1H, CH_2OAc, J=11.8, 8.1 Hz), 4.13 (d, 1H, H-4″, J=9.3 Hz), 2.37 (dd, 1H, H-1′, J=8.1, 6.7 Hz), 2.31 (m, 1H, H-5′), 2.13 (s, 3H, CH_3), 1.65 (m, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 171.0 (CH_3CO), 164.7 (C_6H_5CO), 152.7 (C-2), 151.6 (C-4), 149.5 (C-6), 140.8 (C-8), 133.5 (arom C), 132.7 (arom C), 128.7 (arom C), 127.8 (arom C), 123.4 (C-5), 83.9 (C-2′), 68.4 (C-4′), 59.0 (CH_2OAc), 25.8 (C-1′), 21.8 (C-5′), 21.0 (CH_3),

18.7 (C-6′); Anal. Calcd for $C_{20}H_{19}N_5O_4$ (MW: 393.40): C, 61.06; H, 4.87; N, 17.80. Found: C, 61.14; H, 4.94; N, 17.63.

(1′*R,2′*S**,5′*R**,6′*S**)-9-(6′-Acetyloxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)-2-*N*-acetylguanine (23c) and (1′*R**,2′*S**, 5′*R**,6′*S**)-7-(6′-acetyloxymethyl-3′-oxabicyclo[3.1.0]hex-2′-yl)-2-*N*-acetylguanine (23d).** Compounds **23c** and **23d** were prepared as described for **23a** using BSA (1.30 mL, 5.10 mmol), 2-*N*-acetylguanine (325 mg, 1.68 mmol), diacetate **22** (236 mg, 1.10 mmol) and TMSOTf (238 μL, 1.23 mmol). Both compounds were separated by column chromatography (silica gel, CH_2Cl_2/MeOH: 99/1→96/4) to give isomer **23d** as a white solid (102 mg, 0.29 mmol, 27%) and then isomer **23c** as a white powder (157 mg, 0.45 mmol, 41%).

*Compound **23c***. mp 216–217°C (MeOH); IR (KBr, cm^{-1}) 3126, 1736, 1680, 1614, 1556, 1253; ^1H NMR (DMSOd_6) δ 12.04 (br s, 1H, H1), 11.71 (br s, 1H, N*H*Ac), 8.16 (s, 1H, H-8), 6.06 (s, 1H, H-2′), 4.21 (dd, 1H, C*H*$_2$OAc, *J*=11.8, 7.2 Hz), 4.18–4.11 (m, 2H, C*H*$_2$OAc and H-4′), 3.94 (d, 1H, H-4″, *J*=9.1 Hz), 2.34–2.25 (m, 2H, H-5′ and H-1′), 2.18 (s, 3H, C*H*$_3$CON), 2.06 (s, 3H, C*H*$_3$CO$_2$), 1.54 (m, 1H, H-6′); ^{13}C NMR (DMSOd_6) δ 173.5 (CH$_3$*C*ON), 170.5 (CH$_3$*C*O$_2$), 154.8 (C-6 or C-2), 148.0 (C-4), 147.9 (C-2 or C-6), 137.4 (C-8), 120.2 (C-5), 82.3 (C-2′), 67.2 (C-4′), 59.0 (*C*H$_2$OAc), 25.0 (C-1′), 23.8 (*C*H$_3$CON), 21.2 (C-5′), 20.8 (*C*H$_3$CO$_2$), 17.8 (C-6′); Anal. Calcd for $C_{15}H_{17}N_5O_5{\cdot}0.3H_2O$ (MW: 352.73): C, 51.08; H, 5.03; N, 19.85. Found: C, 50.88; H, 4.91; N, 19.91.

*Compound **23d***. mp 119–120°C; IR (KBr, cm^{-1}) 3153, 1734, 1685, 1614, 1367, 1246; ^1H NMR ($CDCl_3$) δ 12.40 (br s, 1H, NH), 11.16 (br s, 1H, NH), 8.01 (s, 1H, H-8), 6.59 (s, 1H, H-2′), 4.35 (dd, 1H, C*H*$_2$OAc, *J*=11.9, 7.8 Hz), 4.30 (dd, 1H, C*H*$_2$OAc, *J*=11.9, 7.6 Hz), 4.26 (dd, 1H, H-4′, *J*=9.4, 3.6 Hz), 4.15 (d, 1H, H-4″, *J*=9.4 Hz), 2.43 (s, 3H, C*H*$_3$CON), 2.32 (dd, 1H, H-1′, *J*=8.3, 6.6 Hz), 2.21 (m, 1H, H-5′), 2.12 (s, 3H, C*H*$_3$CO$_2$), 1.63 (m, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 173.3 (CH$_3$*C*ON), 171.1 (CH$_3$*C*O$_2$), 156.9 (C-4), 153.2 (C-6 or C-2), 148.1 (C-2 or C-6), 140.3 (C-8), 111.3 (C-5), 85.9 (C-2′), 68.1 (C-4′), 59.0 (*C*H$_2$OAc), 27.0 (C-1′), 24.6 (*C*H$_3$CON), 21.2 (C-5′), 21.0 (*C*H$_3$CO$_2$), 18.6 (C-6′); Anal. Calcd for $C_{15}H_{17}N_5O_5{\cdot}0.3H_2O$ (MW: 352.73): C, 51.08; H, 5.03; N, 19.85. Found: C, 51.09; H, 4.96; N, 19.95.

(1′*R,2′*S**,5′*R**,6′*S**)-9-(6′-Acetyloxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)-2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (23e).** Reaction from BSA (356 μL, 1.40 mmol), 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine (217 mg, 0.56 mmol), diacetate **22** (77 mg, 0.36 mmol) and TMSOTf (80 μL, 0.41 mmol), in the same experimental conditions as for **23a**, led to **23e** as a white solid (118 mg, 0.22 mmol, 61%) after column chromatography (silica gel, CH_2Cl_2/MeOH: 99/1→96/4): mp 170–172°C; IR (KBr, cm^{-1}) 3276, 1736, 1284, 1188; ^1H NMR ($CDCl_3$) δ 8.10 (br s, 1H, NH), 8.04 (s, 1H, H8), 7.50–7.30 (m, 8H, arom), 7.26 (m, 2H, arom), 6.21 (s, 1H, H-2′), 4.37–4.31 (m, 2H, H-4′ and C*H*$_2$OAc), 4.29 (dd, 1H, C*H*$_2$OAc, *J*=11.8, 8.2 Hz), 4.08 (d, 1H, H-4″, *J*=9.2 Hz), 2.50 (s, 3H, CH$_3$), 2.33 (m, 1H, H-5′), 2.26 (dd, 1H, H-1′, *J*=8.2, 6.7 Hz), 2.12 (s, 3H, CH$_3$), 1.61 (m, 1H, H-6′); ^{13}C NMR ($CDCl_3$) δ 171.0 (*C*=O), 170.3 (*C*=O), 156.2 (quat C), 154.5 (quat C), 152.1 (quat C), 150.3 (quat C), 141.9 (*C*H), 141.7 (quat C), 129.2 (*C*H), 127.0 (quat C), 121.2 (quat C), 84.2 (*C*H), 68.7 (*C*H$_2$), 59.1 (*C*H$_2$), 25.9 (*C*H), 25.1 (*C*H$_3$), 22.0 (*C*H), 21.0 (*C*H$_3$), 18.7 (*C*H); HRMS Calcd for $C_{28}H_{26}N_6O_6$: $(M+H)^+$ 543.1992. Found: 543.1988.

(1′*S,2′*S**,5′*R**,6′*S**)-1-(6′-Hydroxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)thymine (11a).** Saturated NH_3 in MeOH (4 mL) was added with stirring to a solution of **23a** (120 mg, 0.43 mmol) in MeOH (4 mL) at 0°C. The mixture was stirred at room temperature for 2 days and the solvent was evaporated in vacuo. Purification of the residue by column chromatography (silica gel, CH_2Cl_2/MeOH: 97/3→96/4) gave the nucleoside **11a** as a white powder (92 mg, 0.39 mmol, 90%): mp 202–204°C (MeOH), IR (KBr, cm^{-1}) 3469, 1691; ^1H NMR (DMSOd_6) δ 11.30 (br s, 1H, NH), 7.41 (d, 1H, H-6, *J*=1.0 Hz), 5.98 (s, 1H, H-2′), 4.60 (dd, 1H, OH, *J*=5.4, 5.4 Hz), 4.22 (dd, 1H, H-4′, *J*=8.8, 4.1 Hz), 3.80 (d, 1H, H-4″, *J*=8.8 Hz), 3.52–3.40 (m, 2H, C*H*$_2$OH), 2.17 (m, 1H, H-5′), 1.89 (dd, 1H, H-1′, *J*=8.3, 6.9 Hz), 1.81 (d, 3H, CH$_3$, *J*=1.0 Hz), 1.30 (m, 1H, H-6′); ^{13}C NMR (DMSOd_6) δ 163.7 (*C*=O), 150.6 (*C*=O), 136.3 (C-6), 109.8 (quat C), 83.7 (C-2′), 68.1 (C-4′), 54.8 (*C*H$_2$OH), 25.5 (C-1′), 21.6 (C-5′), 21.3 (C-6′), 12.2 (*C*H$_3$); Anal. Calcd for $C_{11}H_{14}N_2O_4$ (MW: 238.24): C, 55.46; H, 5.92; N, 11.76. Found: C, 55.48; H, 5.97; N, 11.74.

(1′*S,2′*S**,5′*R**,6′*S**)-9-(6′-Hydroxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)adenine (11b).** Following the same procedure as for the preparation of **11a**, compound **23b** (117 mg, 0.30 mmol) gave, after column chromatography (silica gel, CH_2Cl_2/MeOH: 95/5→90/10), nucleoside **11b** as a white powder (69 mg, 0.28 mmol, 94%): mp 203°C dec. (MeOH); IR (KBr, cm^{-1}) 3357, 1662, 1597; ^1H NMR (DMSOd_6) δ 8.27 (s, 1H, H8), 8.15 (s, 1H, H-2), 7.29 (br s, 2H, NH$_2$), 6.20 (s, 1H, H-2′), 4.63 (dd, 1H, OH, *J*=5.5, 5.5 Hz), 4.20 (dd, 1H, H-4′, *J*=8.7, 3.8 Hz), 3.90 (d, 1H, H-4″, *J*=8.7 Hz), 3.63–3.52 (m, 2H, C*H*$_2$OH), 2.21 (m, 1H, H-5′), 2.14 (dd, 1H, H-1′, *J*=8.1, 6.9 Hz), 1.37 (m, 1H, H-6′); ^{13}C NMR (DMSOd_6) δ 156.0 (C-6), 152.7 (C-2), 148.9 (C-4), 138.7 (C-8), 118.8 (C-5), 82.3 (C-2′), 67.5 (C-4′), 54.8 (*C*H$_2$OH), 25.5 (C-1′), 21.8 (C-6′), 21.4 (C-5′); Anal. Calcd for $C_{11}H_{13}N_5O_2$ (MW: 247.26): C, 53.43; H, 5.30; N, 28.32. Found: C, 53.26; H, 5.23; N, 28.15.

(1′*S,2′*S**,5′*R**,6′*S**)-9-(6′-Hydroxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)guanine (11c).** Saturated NH_3 in MeOH (4 mL) was added with stirring to a solution of **23c** (103 mg, 0.30 mmol) in MeOH (4 mL) at 0°C. The mixture was stirred at room temperature for 2 days and the solvent was evaporated in vacuo. The residue was crystallized in MeOH/H_2O (5/1, 5 mL) to yield nucleoside **11c** as a white powder (57 mg, 0.22 mmol, 73%): mp>315°C (MeOH/H_2O); IR (KBr, cm^{-1}) 3332, 1685, 1655; ^1H NMR (DMSOd_6) δ 10.60 (br s, 1H, H-1), 7.83 (s, 1H, H-8), 6.51 (br s, 2H, NH$_2$), 5.95 (s, 1H, H-2′), 4.59 (dd, 1H, OH, *J*=5.3, 5.3 Hz), 4.12 (dd, 1H, H-4′, *J*=8.8, 3.8 Hz), 3.86 (d, 1H, H-4″, *J*=8.8 Hz), 3.57 (ddd, 1H, C*H*$_2$OH, *J*=11.4, 7.1, 5.3 Hz), 3.49 (ddd, 1H, C*H*$_2$OH, *J*=11.4, 7.9, 5.3 Hz), 2.16 (m, 1H, H-5′), 2.05 (dd, 1H, H-1′, *J*=8.2, 6.9 Hz), 1.33 (m, 1H, H-6′); ^{13}C NMR (DMSOd_6) δ 156.8 (C-6 or C-2), 153.8 (C-2 or C-6), 150.6 (C-4), 134.9 (C-8), 116.5 (C-5), 81.7 (C-2′), 67.2 (C-4′), 54.8 (*C*H$_2$OH), 25.3

(C-1′), 21.6 (C-6′), 21.2 (C-5′); HRMS Calcd for $C_{11}H_{13}N_5O_3$: $(M+H)^+$ 264.1097. Found: 264.1098.

Following the same procedure, compound **23e** (70 mg, 0.13 mmol) gave, after an additional washing of the residue with CH_2Cl_2 (3 mL), nucleoside **11c** as a white powder (24 mg, 0.09 mmol, 71%).

(1′*S,2′*S**,5′*R**,6′*S**)-7-(6′-Hydroxymethyl-3′-oxabicyclo-[3.1.0]hex-2′-yl)guanine (11d).** Following the same procedure as for the preparation of **11c**, compound **23d** (54 mg, 0.15 mmol) gave, after one week stirring, nucleoside **11d** as a white powder (30 mg, 0.11 mmol, 73%): mp 312°C dec. (MeOH/H_2O); IR (KBr, cm^{-1}) 3452, 1683, 1649; ^1H NMR (DMSOd_6) δ 10.87 (br s, 1H, H-1), 8.11 (s, 1H, H-8), 6.36 (s, 1H, H-2′), 6.14 (br s, 2H, NH_2), 4.60 (t, 1H, OH, J=5.4 Hz), 4.06 (dd, 1H, H-4′, J=8.9, 2.0 Hz), 3.87 (d, 1H, H-4″, J=8.9 Hz), 3.52 (dd, 2H, CH_2OH, J=7.3, 5.4 Hz), 2.16–2.10 (m, 2H, H-1′ and H-5′), 1.33 (m, 1H, H-6′); ^{13}C NMR (DMSOd_6) δ 159.8 (quat C), 154.6 (quat C), 152.8 (quat C), 140.7 (C-8), 107.4 (C-5), 84.2 (C-2′), 66.9 (C-4′), 54.7 (*C*H_2OH), 25.8 (C-1′), 21.7 (C-6′), 20.8 (C-5′); HRMS Calcd for $C_{11}H_{13}N_5O_3$: $(M+H)^+$ 264.1097. Found: 264.1092.

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