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Novel Cyclobutane Carbocyclic Nucleosides

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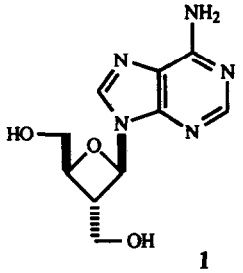
Key words : *Nucleoside analogues ; Oxetanocin carbocyclic analogues ; Selectivity in nucleophilic attack by a nucleic base.*

Abstract : *Epoxidation of cis-3,4-bis(benzyloxymethyl)cyclobut-1-ene **4** gave compounds **7a** and **7b** which were separated. Reaction of the cis-epoxide **7a** with adenine led to the N-9 and N-7 attack products, **10a** and **10b**, respectively. In the same conditions, the trans-epoxide **7b** yielded the N-9 product **12**. Nucleoside analogues **11** and **13** were obtained by debenzylation of **10a** and **12**, respectively.*

Oxetanocin **1** which was isolated from *Bacillus megaterium* in 1986[1] was found to have biological activities, particularly against human immunodeficiency virus HIV.[2] This result led a number of groups to synthesize carbocyclic analogues of this compound.[3] Several of these analogues were found to have interesting biological properties.[3] We began a research program in this area several years ago which led us to describe synthesis of disubstituted cyclobutane products.[4]



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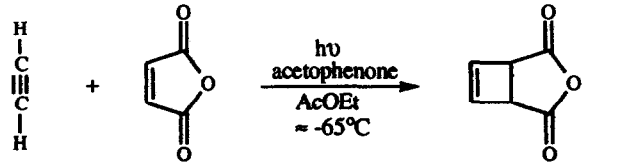
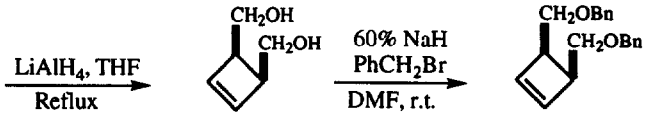
We report in this paper the synthesis of novel trihydroxylated carbocyclic nucleosides **11** and **13** bearing two hydroxymethyl groups in *cis*-position. The starting material was the anhydride **2** prepared by photocycloaddition of acetylene to maleic anhydride.[5] Reduction with lithium aluminium hydride gave the diol **3**[5b] which was benzylated with an excess of benzyl bromide to afford the dibenzyl ether **4** (scheme 1).



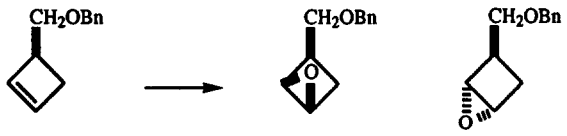
2 ≈ 75%[5]



3 96%[5b] **4** 94%

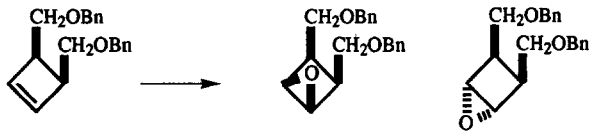
Scheme 1

Several cyclobutene compounds were previously used in epoxidation reactions. For example, in 1989, Zahler and co-workers prepared compounds **6a** and **6b** from the monosubstituted cyclobutene **5** (scheme 2). Reaction with *meta*-chloroperbenzoic acid gave a 64% yield of a 50:50 mixture of **6a** and **6b**. On the other hand a moderate stereoselectivity was observed using Payne's reagent (PhCN, 30% H_2O_2, CH_3OH) (29:71 **6a/6b** ratio in 84% yield). A poor selectivity in epoxidation of a monosubstituted cyclobutene compound with dimethyldioxirane was also reported.[6b] We anticipated a higher selectivity from the disubstituted compound **4**. However reaction with *meta*-chloroperbenzoic acid led to an unexpected result; a slight excess of the more sterically crowded product was produced. This selectivity was reversed with Payne's reagent; reaction led to a **7a/7b** ratio practically equivalent to the **6a/6b** ratio obtained from **5** (scheme 2 and table 1). Both epoxides could be separated by flash chromatography and stereochemistry could be assigned (see below). It is worth mentioning that epoxidation of diol **3** led to an increased selectivity of ≈ 90:10 measured by ^{13}C NMR, the



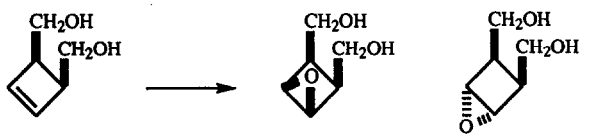
5 **6a** **6b**

m-CPBA/CH_2Cl_2	50 : 50	64%[6a]
Payne's reagent	29 : 71	84%[6a]



4 **7a** **7b**

m-CPBA/CH_2Cl_2	72 : 28	78%
Payne's reagent	35 : 65	62% and 28% of **4** unreacted



3 **8a** **8b**

m-CPBA/CH_2Cl_2	90 : 10	86%

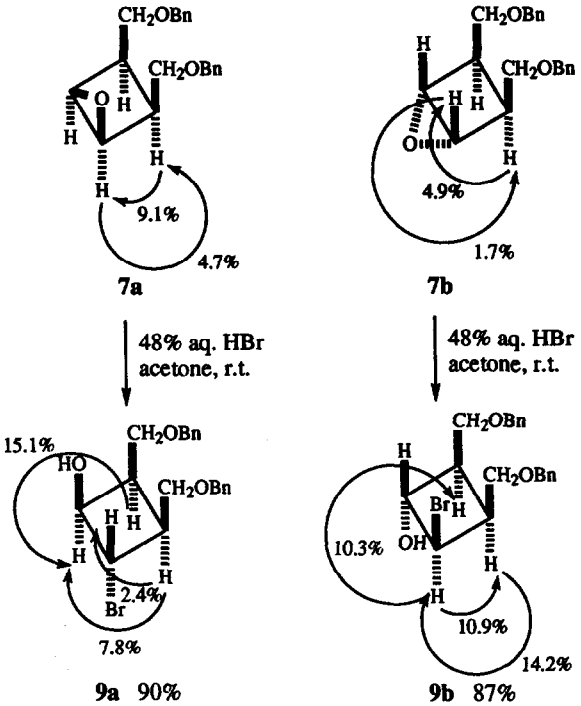
Scheme 2

cis-isomer **8a** where the incoming oxygen is syn to the OH group being presumably predominant.[7] However this result was not useful as separation of both diols **8a** and **8b** was not possible (scheme 2 and table 1).

Olefin epoxidations[a]

Olefin	Reagent	Reaction time	Yield (%)	Ratio of epoxide **a/b**
4	m-CPBA, $NaHCO_3$ in CH_2Cl_2	8h15min	78	72/28[b]
4	m-CPBA, $NaHCO_3$ in CH_3OH	7h15min[c]	-	77/23[b]
4	PhCN, 30% H_2O_2, $KHCO_3$ in CH_3-OH	6 days	62 [d]	35/65[b]
3	m-CPBA, $NaHCO_3$ in CH_2Cl_2	8h	86	90/10[e]

Table 1. [a] At room temperature ; [b] determined by ^1H NMR of the crude mixture ; [c] when methanol was used as the solvent reaction was carried out to 9% completion to avoid ring opening of epoxides ; [d] 28% of **4** didn't react (when reaction was run at a ten fold lower scale the amount of **4** which didn't react was decreased (13%) and selectivity was increased (**7a/7b** = 28:72)) ; [e] determined approximately by ^{13}C NMR.

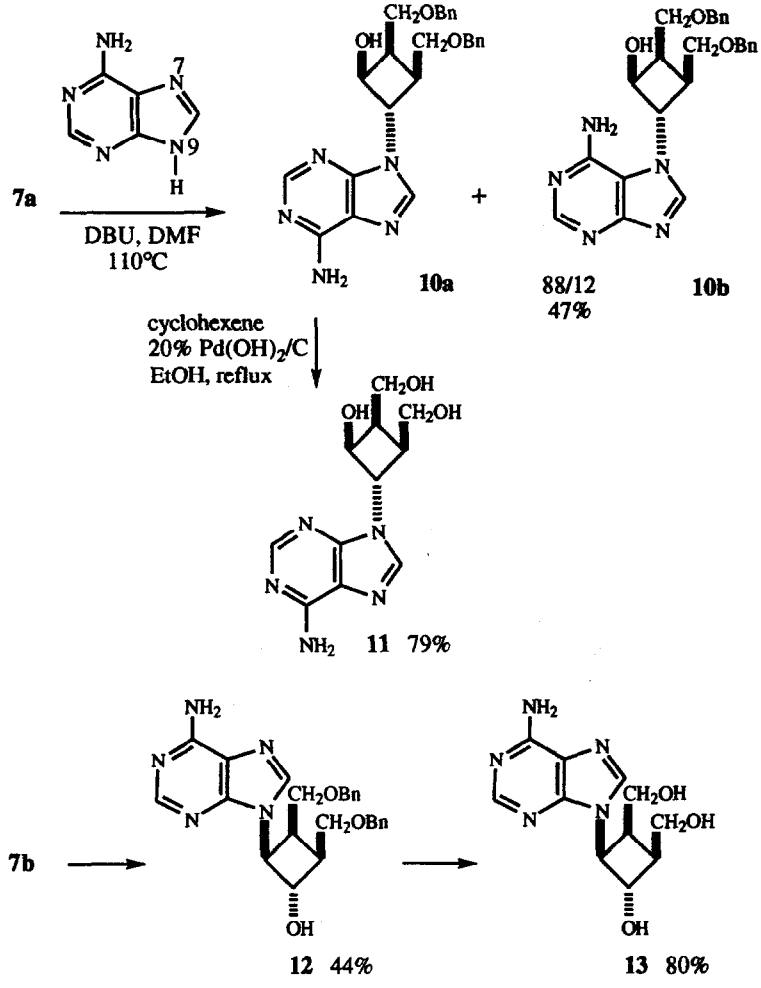


Scheme 3. Selected NOE enhancements

We assumed that **7b** should be predominant in epoxidation with Payne's reagent; however NOE spectra did not give a clear confirmation of this assumption. NOE enhancements were higher for **7a** than for **7b** but

they were not negligible for the last one. This result is consistent with ^1H NMR spectra in which two singlets only were observed in both cases for cyclobutane protons. Therefore dihedral angles and distances are probably nearly the same for **7b** and **7a**. Then we prepared bromohydrins **9a** and **9b** from the corresponding epoxides. These compounds led to strong NOE enhancements for the *cis* relationships and to small or negligible ones for the *trans* ones (scheme 3). Reliable stereochemical assignments for **7a** and **7b** were thus possible.

Reaction of epoxide **7a** with adenine in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N,N*-dimethylformamide at 110°C provided a mixture of products resulting from N-9 (**10a**) and N-7 (**10b**) attack, as shown from the following NMR experiments, in a 88:12 ratio, respectively, and in **47%** yield (scheme 4). Assignments of H_1', H_2', H_3' and H_4' of **10a** were straightforward upon successive ^1H spin decoupling experiments starting from H_2' which is coupled with OH in *d*6-dimethylsulfoxide. Subsequent



Scheme 4

$^{13}C/^{1}H$ correlation and ^{13}C DEPT experiments led to assignment of most ^{13}C signals. However chemical shifts of C_4, C_5 and C_6 could only be obtained through $^{13}C/^{1}H$ COLOC, ^{13}C gated decoupling and ^{13}C with selective ^{1}H decoupling spectra. These experiments also led to measurements of several ^{13}C-^{1}H coupling constants. It was thus pointed out that $H_{1'}$ was coupled with C_4 (J = 1.5 Hz) and C_8 (J = 5.2 Hz). The N-9 attack was thus clearly proved. A similar relationship between $H_{1'}$ and C_8 in **10b** is not compatible with another attack that by N-9 or N-7 and then shows that this compound is the N-7 attack product (on the other hand coupling between $H_{1'}$ and C_5 could not be observed) (figure 1). Data on ^{13}C chemical shifts of both compounds also are in full agreement with previous assignments for related compounds[8] (Compound **10a** : 156.04 (C-6), 152.16 (C-2), 149.69 (C-4), 139.93 (C-8), 119.09 (C-5); compound **10b** : 159.49 (C-4), 152.09 (C-2), 151.78 (C-6), 143.28 (C-8), 111.02 (C-5)).

Cleavage of both benzyl ether groups of **10a** by hydrogenolysis using 20% palladium hydroxide on carbon with cyclohexene as the hydrogen donor[9] gave the nucleoside analogue **11** (scheme 4).

When the isomeric epoxide **7b** was used in the same two-step synthesis, compounds **12** and **13** were successively obtained (scheme 4). NMR experiments showed that the sole substitution product resulted from the N-9 attack (figure 1). Formation of the less crowded product is probably due to the higher steric strain in the nucleophilic attack of **7b**.

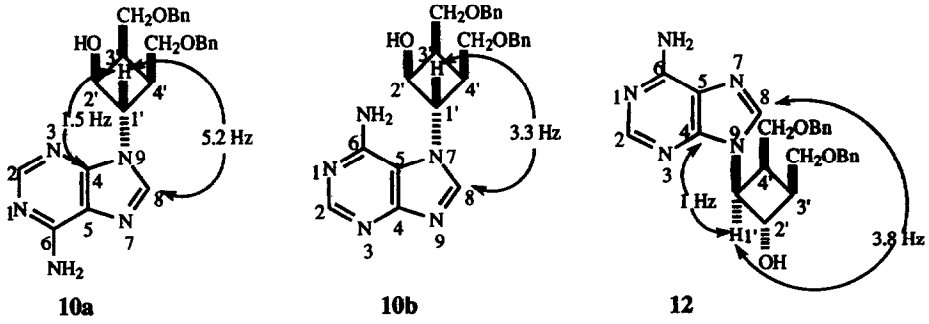


Figure 1

Both nucleoside analogues **11** and **13** have been evaluated as inactive in *in vitro* anti HIV-1 screens (CEM 4 cells) and in inhibition of aspartyl protease of HIV-1.

EXPERIMENTAL SECTION

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AC 400 instrument. Samples were dissolved in deuteriochloroform unless stated, with tetramethylsilane as the internal standard. Multiplicities in the ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded with a Genesis Mattson infrared spectrophotometer. Melting points were determined on a Reichert apparatus and are uncorrected. Elemental analyses were performed by the service de microanalyse, CNRS, ICSN, Gif-sur-Yvette. High resolution mass measurements were performed at the CRMPO (Rennes) with a Varian mat 311 spectrometer. 'Petroleum' refers to a light petroleum fraction, b.p. 40-60°C.

***Cis*-3,4-bis(benzyloxymethyl)cyclobut-1-ene 4**

Sodium hydride (0.54 g of 60% dispersion in mineral oil, prewashed with cyclohexane) was added to a solution of **3** (0.51 g, 4.47 mmol) in dry DMF (5.1 mL) under argon at 0°C. Benzyl bromide (1.30 mL, 10.7 mmol) was added dropwise (the mixture precipitated at 10°C). The reaction mixture was then stirred for 4 h at room temperature. The excess of reagents was destroyed by addition of methanol. After an additional 1 h of stirring, the solvents were evaporated and the residue dissolved in ethyl acetate (11 mL). The resulting solution was washed with water (3 x 2 mL) and brine (2 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was purified by flash chromatography on silica gel (83 g) with cyclohexane-ether (20/1) as eluent. Compound **4** was thus obtained as a colorless oil (1.23 g, 94%). ^1H NMR : δ 7.37-7.24 (m, 10H, phenyl), 6.19 (s, 2H, H-1, H-2), 4.48 (m, 4H, benzylic (AB system), J = 12.5 Hz), 3.66 (dd, 2H, H-5, H-6, J = 9.3, 6.7 Hz), 3.55 (dd, 2H, H-5', H-6', J = 9.3, 6.5 Hz), 3.25 (m, 2H, H-3, H-4). ^{13}C NMR : δ 138.55 (d), 138.46 (s), 128.35 (d), 127.74 (d), 127.54 (d), 73.16 (t), 70.43 (t), 45.51 (d). IR (film) : 3031, 1496, 1454, 1361, 1095, 1027, 734, 696 cm^{-1}. MS : m/z (rel. intensity) : 203 ([M-CH_2Ph]$^+$, 2) ; 107 (6) ; 105 (5) ; 97 (6) ; 92 (6) ; 91 (100) ; 80 (6) ; 79 (7) ; 77 (5) ; 67 (7). HR-MS : calcd for ($C_{20}H_{22}O_2$-CH_2Ph) : 203.1072. Found : 203.1080.

***Cis*-3,*cis*-4-bis(benzyloxymethyl)-1,2-epoxycyclobutane 7a and *trans*-3,*trans*-4-bis(benzyloxymethyl)-1,2-epoxycyclobutane 7b**

m-Chloroperbenzoic acid (1.29 g, 5.60 mmol) was added at 0°C to a solution of **4** (1.5 g, 5.09 mmol) in methylene chloride (15mL) with sodium hydrogen carbonate (174 mg, 2.07 mmol) in suspension. The reaction mixture was stirred at room temperature for 8h15min. Removal of the solvent afforded the crude epoxides as a mixture **7a/7b** = 72/28 measured by ^1H NMR. Flash chromatography on silica gel (350 g) eluting with cyclohexane-ethyl acetate (10/1) gave **7b** (0.35 g, 22.2%) as the first eluted product : m.p. 59-61°C (petroleum). ^1H NMR : δ 7.36-7.25 (m, 10H, phenyl), 4.47 (s, 4H, benzylic), 3.85 (s, 2H, H-1, H-2), 3.69 (dd, 2H, H-5, H-6, J = 9.7, 5.9 Hz), 3.59 (dd, 2H, H-5', H-6', J = 9.7, 8.0 Hz), 2.47 (m, 2H, H-3, H-4). ^{13}C NMR : δ 138.05 (s), 128.45 (d), 127.74 (d), 127.72 (d), 73.22 (t), 66.73 (t), 56.43 (d), 43.07 (d). IR (KBr) : 3025, 1727, 1496, 1454, 1365, 1272, 1087, 748, 700 cm^{-1}. MS : m/z (rel. intensity) : 219 ([M-CH_2Ph]$^+$, 1) ; 113 (2) ; 111 (3) ; 107 (12) ; 105 (3) ; 92 (10) ; 91 (100) ; 83 (4) ; 81 (3) ; 65 (5). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39 ; H, 7.14. Found : C, 76.99 ; H, 7.18. Overlapping fractions contained a mixture of **7a** and **7b** in the 78/22 ratio, respectively (0.14 g, 8.9%). Evaporation of the last fractions gave **7a** as a colorless oil (0.74 g, 46.8%) : ^1H NMR : δ 7.36-7.26 (m, 10H, phenyl), 4.49 (d, 2H, benzylic, J = 11.9 Hz), 4.43 (d, 2H, benzylic, J = 11.9 Hz), 3.90 (s, 2H, H-1, H-2), 3.54 (m, 2H, H-5, H-6), 3.35 (m, 2H, H-5', H-6'), 2,79 (m, 2H, H-3, H-4). ^{13}C NMR : δ 138.27 (s), 128.40 (d), 127.72 (d), 127.64 (d), 73.29 (t), 66.20 (t), 53.10 (d), 41.89 (d). IR (film) : 3030, 1496, 1454, 1365, 1095, 833, 738, 697 cm^{-1}. MS : m/z (rel. intensity) : 219 ([M-CH_2Ph]$^+$, 1) ; 113 (9) ; 111 (2) ; 107 (4) ; 105 (3) ; 92 (8) ; 91 (100) ; 83 (4); 81 (2) ; 65 (4). HR-MS : calcd for ($C_{20}H_{22}O_3$-CH_2Ph) : 219.1021. Found : 219.1015. Epoxidation of **4** (0.100 g, 0.339 mmol) with m-CPBA (86 mg, 0.374 mmol) in the presence of $NaHCO_3$ (12 mg) in MeOH (1 mL) gave a mixture of **7a** and **7b** in the 77/23 ratio, respectively, and 9% of the unreacted starting material (determined by ^1H NMR of the crude mixture) (reaction time : 7h15min). In another experiment benzonitrile (1.22 mL, 11.9 mmol) and $KHCO_3$ (92 mg, 0.92 mmol) were added to a solution of **4** (1 g, 3.39 mmol) in methanol (5 mL).

Hydrogen peroxide (30 wt. % solution in water, 3.89 mL, 38.07 mmol) was then added in 3 portions over 24 h. The reaction mixture was stirred for 6 days, then quenched with a saturated solution of Na_2SO_3 (40 mL). The solvent was evaporated and the residue extracted with methylene chloride (5 x 50 mL). The combined organic phases were washed with a saturated solution of $NaHCO_3$ then brine, and dried ($MgSO_4$). Removal of the solvent afforded the crude epoxides as a mixture **7a/7b** = 35/65 with 28% of the unreacted starting material (measured by ^1H NMR). Flash chromatography on silica gel (235 g) with cyclohexane-ethyl acetate : 10/1 as eluent successively gave the unreacted starting material, epoxide **7b** (0.41 g, 39%), a mixture of **7a** and **7b** in the 68/32 ratio, respectively, (42 mg, 4%) and **7a** (0.20 g, 19%).

Cis-3,_cis_-4-bis(hydroxymethyl)-1,2-epoxycyclobutane 8a and _trans_-3,_trans_-4-bis(hydroxymethyl)-1,2-epoxycyclobutane 8b

m-Chloroperbenzoic acid (2.22 g, 9.64 mmol) was added at 0°C to a solution of **3** (1.0 g, 8.76 mmol) in methylene chloride (10 mL) with sodium hydrogen carbonate (300 mg, 3.57 mmol) in suspension. The reaction mixture was stirred at room temperature for 8h. Solvent evaporation followed by flash chromatography (50% to 100% ethyl acetate/methylene chloride) gave a mixture of **8a** and **8b** as a colorless oil (0.98 g, 86%) in the 90/10 ratio, respectively (approximatively measured by ^{13}C NMR). ^{13}C NMR : δ 59.26, 52.30, 44.17 (**8a**) ; 58.59, 55.19, 45.68 (**8b**).

Cis-3,_cis_-4-bis(benzyloxymethyl)-_trans_-2-bromo-1-hydroxycyclobutane 9a

HBr (48% solution in water, 55 µL, 0.483 mmol) was added to a solution of **7a** (50 mg, 0.161 mmol) in acetone (1.3 mL). Reaction was allowed to proceed for 4h at room temperature then the reaction mixture was neutralized with a saturated solution of $NaHCO_3$ and acetone was evaporated. Residue was extracted with methylene chloride (2 x 5 mL). The combined organic phases were dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (7 g) (cyclohexane-ethyl acetate : 10/1) yielded **9a** (57 mg, 90%) as an oil : ^1H NMR : δ 7.37-7.20 (m, 10H, phenyl), 4.49 (d, 1H, benzylic, J = 12.9 Hz), 4.38 (d, 1H, benzylic, J = 11.4 Hz), 4.36 (m, 1H, H-1, J = 11.0, 7.3 Hz), 4.35 (d, 1H, benzylic, J = 11.8 Hz), 4.30 (d, 1H, benzylic, J = 11.5 Hz), 4.09 (dd, 1H, H-2, J = 9.1, 7.3 Hz), 3.79 (dd, 1H, H-5, J = 9.9, 3.9 Hz), 3.73 (dd, 1H, H-5', J = 9.9, 3.0 Hz), 3.61 (dd, 1H, H-6, J = 9.6, 5.3 Hz), 3.55 (d, 1H, H-6', J = 9.5 Hz), 3.33 (d, 1H, -O<u>H</u>, J = 11.0 Hz), 2.90 (m, 1H, H-4), 2.62 (m, 1H, H-3). ^{13}C NMR : δ 137.96 (s), 136.92 (s), 128.61 (d), 128.41 (d), 128.16 (d), 128.04 (d), 127.98 (d), 127.79 (d), 75.57 (d), 73.64 (t), 73.12 (t), 67.62 (t), 66.59 (t), 50.53 (d), 41.50 (d), 40.79 (d). IR (film) : 3426 (broad), 3029, 1496, 1454, 1365, 1095, 1027, 738, 700 cm^{-1}.

Trans-3,_trans_-4-bis(benzyloxymethyl)-_trans_-2-bromo-1-hydroxycyclobutane 9b

The reaction was performed using the same conditions as described for **9a** from 50 mg (0.161 mmol) of **7b** and 55 µL (0.483 mmol) of 48% aqueous HBr. Crude **9b** was thus obtained (reaction time : 5.5h). Purification by flash chromatography yielded **9b** (55 mg, 87%) : m.p. 94-95°C (ether). ^1H NMR : δ 7.35-7.26 (m, 10H, phenyl), 4.51-4.41 (m, 4H, benzylic), 4.38-4.35 (m, 1H, H-1), 4.29 (dd, 1H, H-2, J = 8.7, 7.5 Hz), 3.76-3.59 (m, 4H, -C<u>H</u>2), 2.73 (m, 1H, H-3), 2.49 (m, 1H, H-4), 2.41 (d, 1H, -O<u>H</u>, J = 5.0 Hz). ^{13}C NMR : δ 138.15 (s), 138.14 (s), 129.62 (d), 128.43 (d), 128.35 (d), 127.77 (d), 127.72 (d), 127.61 (d), 77.77 (d), 73.30 (t), 73.16 (t), 69.09 (t), 68.92 (t), 49.02 (d), 44.07 (d), 34.86 (d). IR (KBr) : 3434 (sharp),

3030, 1371, 1133, 1110, 1072, 1029, 748, 694 cm^{-1}. Anal. Calcd for $C_{20}H_{23}O_3Br$: C, 61.39 ; H, 5.92 ; Br, 20.42. Found : C, 61.15 ; H, 6.14 ; Br, 20.15.

9-[*Trans*-3',*trans*-4'-bis(benzyloxymethyl)-*trans*-2'-hydroxy-cyclobut-1'-yl]adenine 10a and 7-[*Trans*-3',*trans*-4'-bis(benzyloxymethyl)-*trans*-2'-hydroxy-cyclobut-1'-yl]adenine 10b

A solution of **7a** (0.500 g, 1.61 mmol) in DMF (7 mL) was added under argon to a solution of adenine (0.875 g, 6.44 mmol) and DBU (1 mL, 6.44 mmol) in DMF (7 mL). The reaction mixture was stirred at 110°C for 14 h. The DMF was evaporated and the residue dissolved in ethyl acetate (35 mL) was washed with a saturated solution of $NaHCO_3$. The organic phase was dried ($MgSO_4$) and evaporated. ^1H NMR spectrum showed that no starting material remained after 14h and that two analogues of nucleoside **10a** and **10b** were formed in a 88/12 ratio. Flash chromatography (methylene chloride-methanol : 20/1 and 15/1) on silica gel (70 g) gave **10a** as the first eluted product. Recrystallization from methanol gave 0.300 g of **10a** (41.8%) : m.p. 177-178.5°C. ^1H NMR (DMSO-d_6) : δ 8.32 (s, 1H, H-8), 8.16 (s, 1H, H-2), 7.40-7.20 (m, 10H, phenyl), 7.03 (m, 2H, -NH_2), 5.55 (d, 1H, -OH, J = 5.6 Hz), 4.86-4.79 (m, 1H, H-2'), 4.79-4.75 (m, 1H, H-1'), 4.49 (m, 2H, benzylic (AB system), J = 12.3 Hz), 4.30 (m, 2H, benzylic (AB system), J = 12.3 Hz), 3.80-3.68 (m, 3H, -CH_2), 3.58 (m, 1H, -CH_2), 2.94 (m, 1H, H-4'), 2.78 (m, 1H, H-3'). ^{13}C NMR (DMSO-d_6) : δ 156.04 (C-6), 152.16 (C-2), 149.69 (C-4), 139.93 (C-8), 138.50 (s, Ph), 138.36 (s, Ph), 128.20 (d, 2C, Ph), 127.98 (d, Ph), 127.59 (d, Ph), 127.36 (d, 2C, Ph), 127.15 (d, 2C, Ph), 127.08 (d, 2C, Ph), 119.09 (C-5), 72.41 (benzylic), 71.85 (benzylic), 69.11 (-CH_2), 68.76 (C-2'), 66.50 (-CH_2), 60.13 (C-1'), 37.35 (C-3'), 35.99 (C-4'). IR (KBr) : 3446, 3338, 3060, 1623, 1590, 1477, 1367, 1126, 1066, 728, 696 cm^{-1}. MS : m/z (rel. intensity) : 354 ([M-CH_2Ph]$^+$, 8) ; 282 (9) ; 248 (9) ; 176 (9) ; 175 (17) ; 174 (20) ; 136 (15) ; 135 (9) ; 92 (9) ; 91 (100). Anal. Calcd for $C_{25}H_{27}N_5O_3$: C, 67.40 ; H, 6.11 ; N, 15.72. Found : C, 67.50 ; H, 6.07 ; N, 15.72. Product **10b** was eluted later (34 mg, 4.7%) : yellow solid. The following analyses were obtained on a product contaminated by traces of impurities. ^1H NMR (DMSO-d_6) : δ 8.43 (s, 1H, H-8), 8.21 (s, 1H, H-2), 7.37-7.14 (m, 12H, phenyl, -NH_2), 6.45 (d, 1H, -OH, J = 4.4 Hz), 4.82 (m, 1H, H-1'), 4.49 (s, 2H, benzylic), 4.42 (m, 2H, benzylic (AB system), J = 12.6 Hz), 4.37 (m, 1H, H-2'), 3.87-3.69 (m, 4H, -CH_2), 3.12 (m, 1H, H-4'), 2.76 (m, 1H, H-3'). ^{13}C NMR (DMSO-d_6) : δ 159.49 (s), 152.09 (d), 151.78 (s), 143.28 (s), 138.52 (s), 138.29 (s), 128.23, 128.12, 127.47, 127.36, 127.29, 127.16 (d), 111.02 (s), 72.39 (t), 72.20 (t), 69.83 (d), 68.80 (t), 66.47 (t), 61.56 (d), 37.50 (d), 34.16 (d). IR (KBr): 3320, 3099, 1662, 1596, 1315, 1132, 1099, 1051, 752, 698 cm^{-1}.

9-[*cis*-3',*cis*-4'-bis(benzyloxymethyl)-*trans*-2'-hydroxy-cyclobut-1'-yl]adenine 12

The reaction was run according to the procedure described for the preparation of **10a** from 0.730 g (2.35 mmol) of **7b**. ^1H NMR spectrum of the crude mixture showed 4% of the unreacted starting material. Flash chromatography on silica gel (140 g) (methylene chloride-methanol : 20/1) followed by recrystallization from methanol gave **12** (0.46 g, 44%) : m.p. 177-178°C. ^1H NMR (DMSO-d_6) : δ 8.26 (s, 1H, H-8), 8.12 (s, 1H, H-2), 7.38-7.18 (m, 10H, phenyl), 6.85 (broad s, 2H, -NH_2), 5.74 (d, 1H, -OH, J = 6.8 Hz), 4.86 (m, 1H, H-2'), 4.75 (m, 1H, H-1'), 4.51 (d, 1H, benzylic, J = 12.0 Hz), 4.44 (d, 1H, benzylic, J = 12.0 Hz), 4.05 (d, 1H, benzylic, J = 11.5 Hz), 3.98 (d, 1H, benzylic, J = 11.5 Hz), 3.64-3.55 (m, 3H, -CH_2), 3.48-3.44 (m, 1H, -CH_2), 2.79 (m, 1H, H-4'), 2.47 (m, 1H, H-3'). ^{13}C NMR (DMSO-d_6) : δ 155.95 (s), 152.31

(d), 149.96 (s), 139.67 (d), 138.45 (s), 137.82 (s), 128.24 (d), 127.97 (d), 127.67 (d), 127.43 (d), 127.25 (d), 118.87 (s), 72.04 (t, two carbons), 70.17 (d), 68.01 (t), 66.63 (t), 56.22 (d), 41.25 (d), 34.31 (d). IR (KBr) : 3376, 3334, 3156, 1662, 1608, 1571, 1369, 1091, 1049, 727, 700 cm^{-1}. MS : m/z (rel. intensity) : 445 (M^+, 1) ; 354 (12) ; 190 (29) ; 178 (42) ; 175 (12) ; 174 (14) ; 136 (23) ; 135 (13) ; 92 (11) ; 91 (100). Anal. Calcd for $C_{25}H_{27}N_5O_3$: C, 67.40 ; H, 6.11 ; N, 15.72. Found : C, 67.16 ; H, 6.19 ; N, 15.45.

9-[*trans*-3',*trans*-4'-bis(hydroxymethyl)-*trans*-2'-hydroxy-cyclobut-1'-yl]adenine 11

Cyclohexene (6.5 mL) and 20% palladium hydroxide on carbon (0.360 g, moisture ca 50%, prewashed with EtOH, 6 : 10 catalyst/substrate by weight) were added under argon to a solution of **10a** (0.300 g, 0.673 mmol) in ethanol (5.4 mL). The suspension was stirred under reflux for 38h. The catalyst was removed by filtration and the filtrate was evaporated. Purification by flash chromatography on silica gel (33 g) (eluent : methylene chloride-methanol : 8/2) yielded **11** (141 mg, 79%) : m.p. : 200-202°C (methanol). ^1H NMR (DMSO-d_6) : δ 8.25 (s, 1H, H-8), 8.12 (s, 1H, H-2), 7.20 (s, 2H, -NH_2), 5.40 (d, 1H, -CHO<u>H</u>, J = 5.9 Hz), 4.76 (m, 1H, H-2'), 4.61 (m, 1H, H-1', J = 9.2, 7.8 Hz), 4.53 (t, 1H, -CH_2O<u>H</u>, J = 5.3 Hz), 4.48 (t, 1H, -CH_2O<u>H</u>, J = 4.8 Hz), 3.80-3.77 (m, 2H, -<u>CH_2</u>), 3.70-3.65 (m, 1H, -<u>CH_2</u>), 3.60-3.54 (m, 1H, -<u>CH_2</u>), 2.73 (m, 1H, H-4'), 2.61 (m, 1H, H-3'). ^{13}C NMR (DMSO-d_6) : δ 156.03, 152.19, 149.63, 140.05, 119.16, 68.80, 59.95, 59.85, 57.57, 39.29, 38.14. IR (KBr) : 3382, 3320, 3110, 1654, 1602, 1326, 1301, 1033 cm^{-1}. Anal. Calcd for $C_{11}H_{15}O_3N_5$: C, 49.80 ; H, 5.70 ; N, 26.40. Found : C, 49.62 ; H, 5.56 ; N, 26.47.

9-[*cis*-3',*cis*-4'-bis(hydroxymethyl)-*trans*-2'-hydroxy-cyclobut-1'-yl]adenine 13

The reaction was performed using the same conditions as described for **11** from 0.350 g (0.786 mmol) of **12**. Purification by flash chromatography on silica gel (48 g) with methylene chloride-methanol (8/2) then methanol as eluents yielded **13** (0.165 g, 80%) : m.p. 210-211°C (methanol). ^1H NMR (DMSO-d_6) : δ 8.26 (s, 1H, H-8), 8.12 (s, 1H, H-2), 7.16 (broad s, 2H, -NH_2), 5.57 (d, 1H, -CHO<u>H</u>, J = 6.7 Hz), 4.75 (m, 1H, H-2'), 4.68 (m, 1H, H-1'), 4.56 (t, 1H, -CH_2O<u>H</u>, J = 5.2 Hz), 4.45 (t, 1H, -CH_2O<u>H</u>, J = 4.4 Hz), 3.66 (m, 2H, -<u>CH_2</u>), 3.57 (m, 1H, -<u>CH_2</u>), 3.40 (m, 1H, -<u>CH_2</u>), 2.64 (m, 1H, H-4'), 2.27 (m, 1H, H-3'). ^{13}C NMR (DMSO-d_6) : δ 155.88 (s), 152.30 (d), 149.91 (s), 140.03 (d), 118.88 (s), 70.21 (d), 59.28 (t), 57.53 (t), 55.99 (d), 43.86 (d), 36.28 (d). IR (KBr) : 3365, 3129, 1673, 1610, 1571, 1334, 1018 cm^{-1}. Anal. Calcd for $C_{11}H_{15}O_3N_5$: C, 49.80 ; H, 5.70 ; N, 26.40. Found : C, 49.40 ; H, 5.49 ; N, 26.01.

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