Selective Synthesis of a Novel Methylenecyclobutane Nucleoside Analogue

Noëlle Gauvry,[a] Laxminarayan Bhat,[a] Laurence Mévellec,[a] Martine Zucco,[b] and François Huet*[a]

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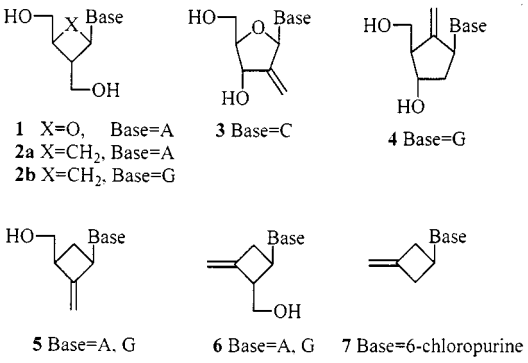
Nucleophilic ring-opening of the unsymmetrical cyclobutyl epoxide **10a** by adenine yielded a mixture of three nucleoside compounds **9a**–**c**. Their structures have been elucidated with the aid of various NMR techniques, in particular by heteronuclear multiple bond correlation (HMBC). The major isomer was selectively benzylated at the secondary hydroxyl group to afford **13**. Subsequent mesylation of the hydroxymethyl group, followed by conversion into an *o*-nitrophenylselenide and oxidation yielded the elimination product **16**. Deprotection with boron trichloride provided the novel methylenecyclobutane nucleoside analogue **8**.

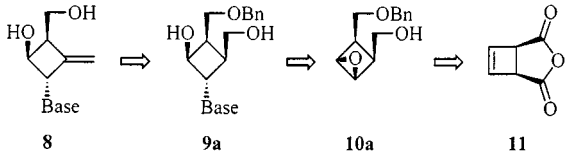
Introduction

Since oxetanocin A[1] **1** was isolated from *Bacillus megaterium*, the synthesis and evaluation of its carbocyclic analogues, cyclobut-A **2a** and cyclobut-G **2b**, have been reported by many groups, either as racemates[2] or as individual enantiomers[3] (Scheme 1). Due to the promising antiviral properties of these two compounds, numerous cyclobutane nucleoside analogues bearing different functional groups (OH, F, N_3, alkyl...) have been prepared.[4] Although nucleosides with an exocyclic double bond such as 2′-deoxy-2′-methylidenecytidine (DMDC) **3**[5] and BMS-200475 **4**[6] exhibit interesting biological activities, only a few methylene-substituted cyclobutyl analogues have been described, e.g. **5**, **6**, and **7**.[7]



Scheme 1. Nucleoside analogues

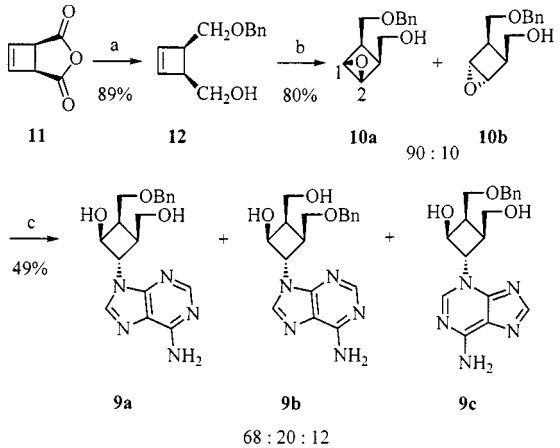
We have recently obtained the unsymmetrical epoxide **10a**[8] in a highly selective manner in three steps, starting from *cis*-cyclobut-3-ene-1,2-dicarboxylic anhydride **11**.[9] This compound appeared to be very interesting from a synthetic point of view. A degree of regioselectivity in the course of nucleophilic attack of compounds such as adenine was indeed conceivable due to a control by intramolecular hydrogen bonding in **10a**. Subsequent elimination of the primary hydroxyl group could be envisaged as leading to the novel methylenecyclobutane nucleoside analogue **8** (Scheme 2).



Scheme 2. Retrosynthetic analysis

Results and Discussion

In previous work,[8] anhydride **11**[9] was reduced to the corresponding diol, which was then monobenzylated to give **12** (Scheme 3). Treatment of the latter compound with *m*-CPBA yielded predominantly the epoxide **10a** along with **10b**; the **10a**:**10b** ratio was found to be 78:22 in the crude mixture and 90:10 after purification by chromatography.



Scheme 3. Synthesis and nucleophilic ring-opening of epoxide **10a**: (a) i. $LiAlH_4$, THF, reflux, ii. $PhCH_2Br$, NaH, DMF; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2; (c) adenine, DBU, DMF, 110 °C

[a] Laboratoire de Synthèse Organique, UPRES A CNRS 6011, Université du Maine,
avenue Olivier Messiaen, F-72085 Le Mans Cedex 9, France
Fax: (internat.) +33-2/4383-3366
E-mail: fhuet@aviion.univ-lemans.fr
[b] Rhône-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, 13, quai Jules Guesde, BP14-zone C, F-94403 Vitry-sur-Seine Cedex, France

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Nucleophilic Ring Opening of Epoxide 10a

Separation of **10a** and **10b** proved to be possible by column chromatography, although not very easy. We therefore examined the reaction of the mixture of racemic epoxides **10a/10b** (90:10) with adenine in DMF in the presence of DBU at 110 °C. After 14 h, three products **9a/9b/9c** had been generated in a 68:20:12 ratio and in 49% overall yield. A similar experiment performed using a sample of pure epoxide **10a** afforded the same product mixture, showing the minor epoxide **10b** to be unreactive under these coupling conditions. The formation of several isomers was not surprising considering that adenine possesses several nucleophilic centers and there are two possible sites of attack on the oxirane. Complete separation of **9a**, **9b**, and **9c** could not be achieved by column chromatography. Nevertheless, we succeeded in obtaining a pure sample of **9a** by recrystallization of the mixture from methanol, as well as enriched samples of **9b** and **9c**. At this point, structure elucidations were carried out by means of various NMR experiments, in particular by $^{1}H/^{13}C$ heteronuclear long-range correlations (HMBC) (Figure 1).

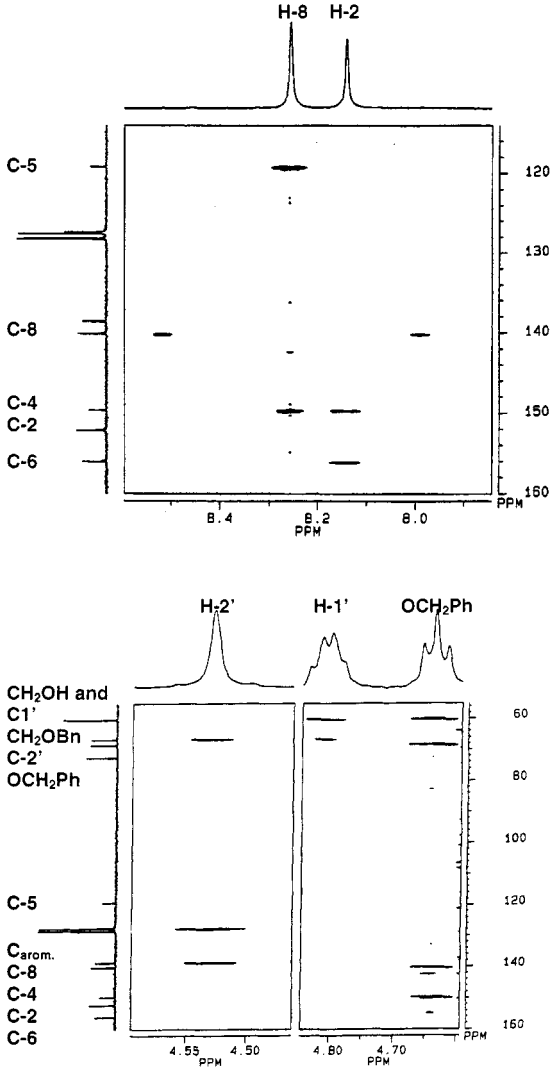
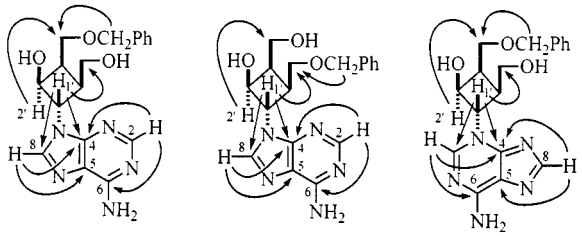


Figure 1. HMBC spectrum of **9a** recorded in [D_6]DMSO

To distinguish between the potential sites of adduct formation on adenine, the unambiguous assignment of the signals of its protons and carbon atoms was required.[10] In adenine derivatives, C-5 always resonates at higher field than the other carbons as it is only linked to one nitrogen rather than two. It was thus easily identified for each product **9a–c**, and its correlation with 8-H, but not with 2-H, made it possible to assign these two protons. On this basis, a ^{1}J $^{13}C/^{1}H$ correlation led to assignments of the corresponding carbons (C-2 and C-8). The signals due to C-6 and C-4 could then be distinguished in that they show long-range couplings with 2-H only, and with 2-H and 8-H, respectively. Finally, correlations between 1′-H and two quaternary carbons of the nucleobase in each case indicate that **9a** and **9b** stem from attack at N-9, while **9c** is formed through an attack at N-3 (Figure 2).



9a **9b** **9c**

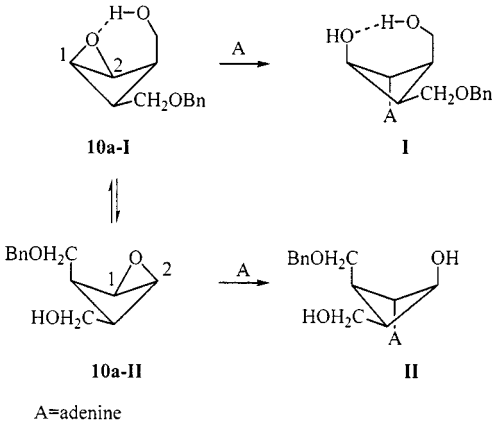
Figure 2. Relevant HMBC correlations for **9a**, **9b**, and **9c**

To elucidate the regiochemistry of the oxirane ring-opening, we also examined the long-range correlations. Firstly, the signals due to 1′-H and 2′-H were assigned by proton-decoupling experiments. The DEPT-135 spectrum allowed the identification of the CH_2 signals, then those due to CH_2OH and CH_2OBn could be distinguished as only the latter show a long-range interaction with the benzylic protons. Finally, from ^{3}J correlations between 1′-H or 2′-H and CH_2OH or CH_2OBn, it could be ascertained whether the ring-opening occurs at C-1 or C-2 of epoxide **10a**. Thus, compounds **9a** and **9c** were found to result from an attack of adenine at C-2, while **9b** stems from an attack at C-1.

As expected, regiocontrol in favor of attack at C-2 as opposed to C-1 (80:20) is observed. This is consistent with the presence of a hydrogen bond only in the conformation **10a–I**, which is thus likely to predominate (Scheme 4). The subsequent ring-opening process may occur in a *trans pseudo*-diaxial manner, as is well-known for epoxides fused to a cyclohexane ring.[11] Therefore, the major products are of type **I**.

Synthesis of Methylenecyclobutane Nucleoside Analogue 8

The next step was elimination of the primary hydroxyl group of compounds **9a–c**. We first attempted to use the same method as Maruyama and co-workers,[7a][7b] i.e. to convert the mixture of compounds **9a–c** into their iodide

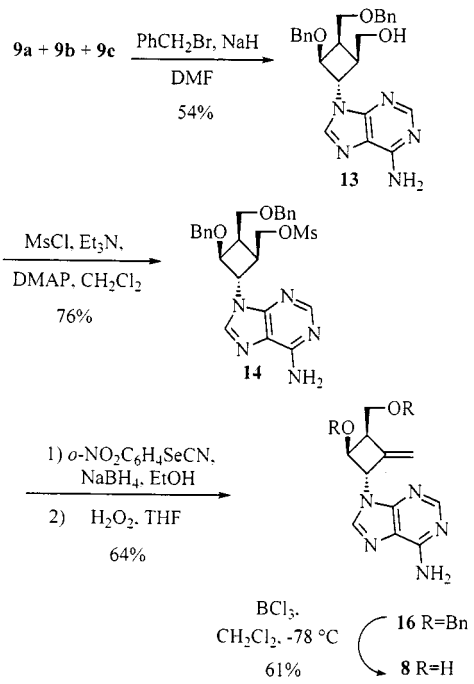


Scheme 4. Possible explanation for the observed regiocontrol during the ring-opening step

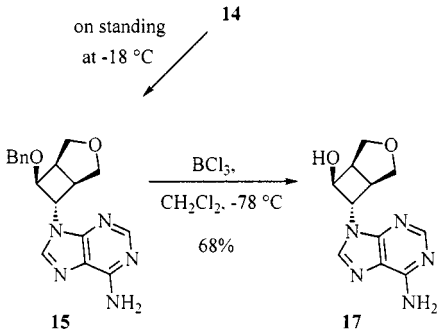
derivatives with the Rydon reagent[12] and then to use *t*BuOK in an elimination step. However, this method was unsuccessful in the present case. Numerous attempts to convert the hydroxyl group into iodide or other good leaving groups (OMs, OTs, Br, SeR...) under standard conditions also met with failure, leading only to recovery of the starting material. The poor reactivities of compounds **9a−c**, which may stem from their very low solubilities in organic solvents, could not be compensated for by using reagents in excess in view of the need for selectivity between the primary and secondary hydroxyl groups.

Eventually, it was found that treatment of compounds **9a−c** with benzyl bromide in the presence of NaH in DMF provides the benzylated compound **13**. Surprisingly, benzylation occurs selectively at the secondary hydroxyl group (Scheme 5). This selectivity may be rationalized in terms of preferential hydrogen-bonding of the primary hydroxyl group, rendering the proton of the secondary hydroxyl group more acidic. The structure of **13** was elucidated on the basis of its ^{1}H NMR spectrum in [D$_6$]DMSO, which features a triplet due to the remaining free hydroxyl proton in accordance with a hydroxymethyl group. Fortunately, compound **13** could be isolated as a single isomer, i.e. that arising from benzylation of the major product of ring-opening, **9a**. Furthermore, it was found to be soluble in chloroform and could thus be converted into mesylate **14** using an excess of mesyl chloride in the presence of Et$_3$N and 4-dimethylaminopyridine. Elimination of methanesulfonic acid from **14** by treatment with *t*BuOK or *n*Bu$_4$NF does not afford the expected product. On the other hand, this compound undergoes spontaneous transformation to **15** within several hours, even at low temperature (Scheme 6). Debenzylation of **15** with boron trichloride at −78 °C yields the bicyclic analogue **17**.

As the attempted transformation to a methylenecyclobutane derivative through a one-step elimination from mesylate **14** met with failure, we carried out a substitution to give the *o*-nitrophenylselenide;[13] subsequent oxidation of the latter with H$_2$O$_2$ yielded the *exo*-methylene derivative **16**. Finally, a similar deprotection as above furnished the target nucleoside analogue **8**.



Scheme 5. Synthesis of target nucleoside analogue **8** (isolated yield of **13** based on the amount of **9a** in the **9a/9b/9c** mixture)



Scheme 6. Synthesis of bicyclic analogue **17**

Conclusion

In conclusion, we have obtained a new methylenecyclobutane nucleoside analogue **8**. Our strategy involved several regio- and stereoselective steps. Extensive NMR studies were required in order to identify all the products derived from reaction of adenine with epoxides **10a/10b**. We also took advantage of an unexpected substitution of **14** to prepare the bicyclic nucleoside analogue **17**. Biological tests have shown that compounds **8** and **17** do not exhibit antitumor properties.

Experimental Section

General Remarks: All moisture-sensitive reactions were carried out in oven-dried glassware (100 °C) under nitrogen atmosphere. − Commercially available reagents and solvents were purified and dried, when necessary, by standard methods immediately prior to

use. − All melting points are uncorrected. − IR spectra were recorded on an FT-IR spectrophotometer (ATI-Mattson Genesis). − ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument at 400 and 100.6 MHz, respectively; chemical shifts are reported in ppm downfield from TMS used as an internal standard. − Elemental analyses were provided by the Service de Microanalyse, CNRS ICSN, Gif-sur-Yvette. − High-resolution mass spectral measurements were performed at the CRMPO, Rennes.

Compounds 9: A solution of epoxides **10**[8] (**10a/10b**, 90:10, 4.00 g, 18.2 mmol) in dry DMF (55 mL) was added dropwise to a mixture of adenine (9.80 g, 72.5 mmol) and DBU (10.8 mL, 72.2 mmol) in dry DMF (55 mL). The resulting mixture was stirred at 110 °C for 17 h and then the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 99:1 to 95:5) to yield a mixture of three isomers **9a/9b/9c** (2.84 g, 49% based on **10a**) in a 68:20:12 ratio as a pale-yellow solid. An analytical sample of **9a** was obtained by recrystallization from methanol, whereas the other isomers were analyzed as enriched mixtures.

(1′*S,2′*S**,3′*R**,4′*R**)-9-(3′-Benzyloxymethyl-2′-hydroxy-4′-hydroxymethylcyclobut-1′-yl)adenine (9a):** White solid; m.p. 221−222 °C (methanol). − IR (KBr): $\tilde{\nu}$ = 3295 cm^{-1}, 3162, 1702, 1616, 1116, 1027, 732. − ^{1}H NMR ([D$_6$]DMSO): δ = 2.75 (m, 2 H, 3′-H and 4′-H), 3.54 (m, 1 H, C*H*$_2$OH), 3.67 (m, 1 H, C*H*$_2$OH), 3.72−3.79 (m, 2 H, C*H*$_2$OBn), 4.35 (t, *J* = 4.7 Hz, 1 H, CH$_2$O*H*), 4.52 (m, 2 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.62 (m, 1 H, 1′-H), 4.79 (m, 1 H, 2′-H), 5.46 (d, *J* = 5.4 Hz, 1 H, CHO*H*), 7.20 (br. s, 2 H, NH$_2$), 7.30−7.38 (m, 5 H, C$_6$H$_5$), 8.13 (s, 1 H, 2-H), 8.24 (s, 1 H, 8-H). − ^{13}C NMR ([D$_6$]DMSO): δ = 37.4 (C-3′ or C-4′), 38.1 (C-3′ or C-4′), 60.2 (*C*H$_2$OH and C-1′), 66.6 (*C*H$_2$OBn), 68.4 (C-2′), 72.5 (O*C*H$_2$C$_6$H$_5$), 119.2 (C-5), 127.4 (C$_6$H$_5$), 127.6 (C$_6$H$_5$), 128.3 (C$_6$H$_5$), 138.6 (C$_6$H$_5$), 140.1 (C-8), 149.6 (C-4), 152.2 (C-2), 156.0 (C-6). − $C_{18}H_{21}N_5O_3$ (355.4): calcd. C 60.83, H 5.96, N 19.71; found C 60.74, H 5.81, N 19.46.

(1′*R,2′*R**,3′*S**,4′*S**)-9-(4′-Benzyloxymethyl-2′-hydroxy-3′-hydroxymethylcyclobut-1′-yl)adenine (9b):** ^{1}H NMR ([D$_6$]DMSO): δ = 2.90 (m, 2 H, 3′-H and 4′-H), 3.60−3.80 (m, 5 H, CH$_2$ and CH$_2$O*H*), 4.32 (m, 2 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.75−4.80 (m, 2 H, 2′-H and 1′-H), 5.46 (br. s, 1 H, CHO*H*), 7.20 (br. s, 2 H, NH$_2$), 7.30−7.38 (m, 5 H, C$_6$H$_5$), 8.14 (s, 1 H, 2-H), 8.31 (s, 1 H, 8-H). − ^{13}C NMR ([D$_6$]DMSO): δ = 35.8 (C-3′ or C-4′), 36.1 (C-3′ or C-4′), 57.6 (*C*H$_2$OH), 60.4 (C-1′), 69.2 (*C*H$_2$OBn), 69.3 (C-2′), 71.8 (O*C*H$_2$C$_6$H$_5$), 119.1 (C-5), 127.0 (C$_6$H$_5$), 127.2 (C$_6$H$_5$), 128.0 (C$_6$H$_5$), 138.5 (C$_6$H$_5$), 140.0 (C-8), 149.7 (C-4), 152.3 (C-2), 156.0 (C-6). − HRMS FAB ($C_{18}H_{22}N_5O_3$): calcd. 356.1723; found 356.1725 [M + H].

(1′*S,2′*S**,3′*R**,4′*R**)-3-(3′-Benzyloxymethyl-2′-hydroxy-4′-hydroxymethylcyclobut-1′-yl)adenine (9c):** ^{1}H NMR ([D$_6$]DMSO): δ = 2.61 (m, 1 H, 3′-H), 3.17 (m, 1 H, 4′-H), 3.60−3.80 (m, 4 H, CH$_2$), 4.14 (br. s, 1 H, CH$_2$O*H*), 4.35 (m, 2 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.75 (m, 1 H, 1′-H), 4.94 (m, 1 H, 2′-H), 5.76 (br. s, 1 H, CHO*H*), 7.10−7.40 (m, 7 H, C$_6$H$_5$ and NH$_2$), 7.78 (s, 1 H, 8-H), 8.43 (s, 1 H, 2-H). − ^{13}C NMR ([D$_6$]DMSO): δ = 34.1 (C-4′), 38.0 (C-3′), 57.5 (CH$_2$), 66.9 (C-1′), 67.5 (C-2′), 69.3 (CH$_2$), 71.9 (O*C*H$_2$C$_6$H$_5$), 120.4 (C-5), 127.4 (C$_6$H$_5$), 128.1 (C$_6$H$_5$), 131.6 (C$_6$H$_5$), 138.3 (C$_6$H$_5$), 142.4 (C-2), 149.4 (C-4), 152.0 (C-8), 154.8 (C-6). − HRMS FAB ($C_{18}H_{22}N_5O_3$): calcd. 356.1723; found 356.1734 [M + H].

(1′*S,2′*S**,3′*R**,4′*R**)-9-(2′-Benzyloxy-3′-benzyloxymethyl-4′-hydroxymethylcyclobut-1′-yl)adenine (13):** To a cooled mixture (0 °C) of compounds **9a/9b/9c** (68:20:12, 1.10 g, 3.1 mmol) in dry DMF (7 mL) was slowly added 60% NaH (186 mg, 4.6 mmol). The reaction mixture was stirred at 0 °C for 30 min. and then benzyl bromide (0.4 mL, 3.4 mmol) was added dropwise. The resulting mixture was stirred at room temp. for 15 h. Methanol (5 mL) was then added and the mixture was concentrated to dryness. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 98:2 to 96:4) to afford **13** (506 mg, 54% based on **9a**) as white crystals; m.p. 168−169 °C (EtOAc/light petroleum). − IR (KBr): $\tilde{\nu}$ = 3276 cm^{-1}, 3143, 1694, 1608, 1095, 1026, 732, 698. − ^{1}H NMR (CDCl$_3$): δ = 2.78 (m, 1 H, 3′-H or 4′-H), 3.10 (m, 1 H, 3′-H or 4′-H), 3.77−3.92 (m, 4 H, CH$_2$), 4.23 (br. s, 1 H, OH), 4.43 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.54 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.56 (d, *J* = 11.5 Hz, 1 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.61 (d, *J* = 11.5 Hz, 1 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.68 (m, 2 H, 1′-H and 2′-H), 5.74 (br. s, 2 H, NH$_2$), 7.15−7.39 (m, 10 H, C$_6$H$_5$), 7.59 (s, 1 H, 2-H), 8.31 (s, 1 H, 8-H). − ^{13}C NMR (CDCl$_3$): δ = 37.2 (C-3′ or C-4′), 38.8 (C-3′ or C-4′), 58.4 (C-1′ or C-2′), 60.8 (*C*H$_2$OH), 66.3 (*C*H$_2$OBn), 72.1 (O*C*H$_2$C$_6$H$_5$), 73.9 (C-1′ or C-2′), 74.3 (O*C*H$_2$C$_6$H$_5$), 120.0 (C-5), 127.8 (C$_6$H$_5$), 127.98 (C$_6$H$_5$), 128.00 (C$_6$H$_5$), 128.05 (C$_6$H$_5$), 128.4 (C$_6$H$_5$), 128.5 (C$_6$H$_5$), 137.2 (C$_6$H$_5$), 137.3 (C$_6$H$_5$), 138.7 (C-8), 149.7 (C-4), 152.6 (C-2), 155.6 (C-6). − $C_{25}H_{27}N_5O_3$ (445.5): calcd. C 67.40, H 6.11, N 15.72; found C 67.18, H 6.09, N 15.47.

(1′*S,2′*S**,3′*R**,4′*R**)-9-(2′-Benzyloxy-3′-benzyloxymethyl-4′-methanesulfonyloxymethylcyclobut-1′-yl)adenine (14):** Et$_3$N (0.38 mL, 2.7 mmol), 4-DMAP (0.33 g, 2.7 mmol), and MsCl (0.42 mL, 5.5 mmol) were slowly added to a solution of **13** (0.61 g, 1.4 mmol) in CHCl$_3$ (6 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C followed by 12 h at room temp., and then concentrated to dryness. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5) to yield **14** (0.54 g, 76%) as a yellow oil. − IR (neat): $\tilde{\nu}$ = 3284 cm^{-1}, 3156, 1695, 1100, 1022, 735, 700. − ^{1}H NMR (CDCl$_3$): δ = 2.76 (s, 3 H, CH$_3$), 3.08 (m, 1 H, 4′-H), 3.26 (m, 1 H, 3′-H), 3.80 (m, 2 H, 6′-H and 6′′-H), 4.35−4.57 (m, 6 H, OC*H*$_2$C$_6$H$_5$, 5′-H and 5′′-H), 4.83 (dd, *J* = 7.8, 7.8 Hz, 1 H, 1′-H), 4.99 (dd, *J* = 7.8, 7.8 Hz, 1 H, 2′-H), 5.70 (br. s, 2 H, NH$_2$), 7.08−7.38 (m, 10 H, C$_6$H$_5$), 7.60 (s, 1 H, 2-H or 8-H), 8.29 (s, 1 H, 2-H or 8-H). This compound had to be purified by flash chromatography and then used as quickly as possible for the next step to avoid intramolecular substitution leading to **15**.

(1′*R,5′*R**,6′*S**,7′*S**)-9-(7′-Benzyloxy-3′-oxabicyclo[3.2.0]hept-6′-yl)adenine (15):** IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1}, 3342, 1654, 1637, 1602, 1475, 1328, 1110, 1037. − ^{1}H NMR (CDCl$_3$): δ = 3.30 (m, 1 H, 1′-H), 3.41 (m, 1 H, 5′-H), 3.48 (dd, *J* = 9.4, 4.0 Hz, 1 H, 4′-H), 3.64 (dd, *J* = 9.4, 7.4 Hz, 1 H, 2′-H), 3.97 (m, 1 H, 4′′-H), 4.38 (dd, *J* = 9.4, 1.7 Hz, 1 H, 2′′-H), 4.39 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.46 (d, *J* = 12.0 Hz, 1 H, OC*H*$_2$C$_6$H$_5$ AB system), 4.49 (m, 1 H, 6′-H), 4.82 (dd, *J* = 7.4, 7.4 Hz, 1 H, 7′-H), 5.59 (br. s, 2 H, NH$_2$), 7.17−7.25 (m, 5 H, C$_6$H$_5$), 7.53 (s, 1 H, 2-H or 8-H), 8.34 (s, 1 H, 2-H or 8-H). − ^{13}C NMR (CDCl$_3$): δ = 39.5 (C-1′), 40.2 (C-5′), 59.6 (C-6′), 66.4 (C-2′), 71.0 (C-4′), 71.2 (O*C*H$_2$C$_6$H$_5$), 74.0 (C-7′), 120.2 (C-5), 127.7 (C$_6$H$_5$), 127.9 (C$_6$H$_5$), 128.3 (C$_6$H$_5$), 137.4 (C$_6$H$_5$), 139.8 (C-8), 150.2 (C-4), 152.7 (C-2), 155.7 (C-6). − HRMS ($C_{18}H_{20}N_5O_2$): calcd. 338.1617; found 338.1616 [M + H].

(1′*S,2′*S**,3′*R**)-9-(2′-Benzyloxy-3′-benzyloxymethyl-4′-methylenecyclobut-1′-yl)adenine (16):** NaBH$_4$ (40 mg, 1.1 mmol) was added to a mixture of *o*-nitrophenylselenocyanate (271 mg, 1.0 mmol) and dry EtOH (1.5 mL) at −5 °C. The mixture was stirred at room temp. until a solution was obtained and then co-

oled to −5 °C once more. A solution of **14** (250 mg, 0.5 mmol) in dry EtOH (0.5 mL) was then added dropwise and the resulting mixture was stirred at room temp. for 24 h. The suspension obtained was cooled to 0 °C, THF (1 mL) and H_2O_2 (35% v/v, 0.84 mL, 9.5 mmol) were added, and the mixture was stirred at room temp. for 24 h. After evaporation of the solvents, the residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 98:2 then 95:5) to afford **16** (131 mg, 64%) as a pale-yellow oil contaminated by residual selenium. − IR (neat): $\tilde{\nu}$ = 3300 cm^{-1}, 3145, 1603, 1575, 1098, 1035, 730, 700. − ^1H NMR ($CDCl_3$): δ = 3.48 (m, 1 H, 3′-H), 3.70−3.96 (m, 2 H, CH_2OBn), 4.51−4.60 (m, 5 H, $OCH_2C_6H_5$ and 2′-H), 5.06 (br. s, 1 H, 5′-H), 5.35 (br. s, 1 H, 5′′-H), 5.64 (m, 1 H, 1′-H), 6.25 (br. s, 2 H, NH_2), 7.10−7.35 (m, 10 H, C_6H_5), 7.77 (s, 1 H, 2-H or 8-H), 8.30 (s, 1 H, 2-H or 8-H). − HRMS ($C_{25}H_{26}N_5O_2$): calcd. 428.2086; found 428.2081 [M + H].

(1′*S,2′*S**,3′*R**)-9-(2′-Hydroxy-3′-hydroxymethyl-4′-methylenecyclobut-1′-yl)adenine (8):** A solution of compound **16** (85 mg, 0.2 mmol) in dry CH_2Cl_2 (6 mL) was cooled to −78 °C. A 1 M solution of BCl_3 in CH_2Cl_2 (4.4 mL, 4.4 mmol) was added dropwise and the mixture was stirred for 6 h at −78 °C. MeOH (5 mL) was then carefully added, and the mixture was allowed to warm to room temp. and concentrated. The residue was dried by co-evaporation three times with MeOH (5 mL). A further portion of MeOH (5 mL) was then added and the resulting solution was neutralized with a saturated solution of NH_3 in MeOH. The solvent was then completely removed from the suspension obtained. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 99:1 to 93:7) to afford, after recrystallization from MeOH, **8** (30 mg, 61%) as a white solid; m.p. 198−199 °C. − IR (KBr): $\tilde{\nu}$ = 3434 cm^{-1}, 3328, 3180, 1662, 1604, 1571, 1483, 1307, 1153, 1035. − ^1H NMR ([D$_6$]DMSO): δ = 3.12 (m, 1 H, 3′-H), 3.67 (m, 1 H, 6′-H), 3.82 (m, 1 H, 6′′-H), 4.52 (t, *J* = 5.2 Hz, 1 H, CH_2OH), 4.80 (br. s, 1 H, 5′-H), 4.89 (m, 1 H, 2′-H), 5.11 (br. s, 1 H, 5′′-H), 5.44 (m, 1 H, 1′-H), 5.64 (d, *J* = 5.9 Hz, 1 H, CHO*H*), 7.23 (br. s, 2 H, NH_2), 8.13 (s, 1 H, 8-H or 2-H), 8.23 (s, 1 H, 8-H or 2-H). − ^{13}C NMR ([D$_6$]DMSO): δ = 47.8 (C-3′), 59.5 (C-6′), 62.6 (C-1′ or C-2′), 69.3 (C-1′ or C-2′), 108.6 (C-5′), 118.7 (C-5), 139.6 (C-4′), 145.0 (C-8), 149.5 (C-4), 152.4 (C-2), 156.0 (C-6). − HRMS ($C_{11}H_{14}N_5O_2$): calcd. 248.1147; found 248.1154 [M + H].

(1′*R,5′*R**,6′*S**,7′*S**)-9-(7′-Hydroxy-3′-oxabicyclo[3.2.0]hept-6′-yl)adenine (17):** A solution of **15** (90 mg, 0.3 mmol) in dry CH_2Cl_2 (8 mL) was cooled to −78 °C. A 1 M solution of BCl_3 in CH_2Cl_2 (3.0 mL, 3.0 mmol) was added dropwise and the mixture was stirred for 6 h at −78 °C. MeOH (5 mL) was then carefully added, and the mixture was allowed to warm to room temp. and concentrated. The residue was dried by co-evaporation three times with MeOH (5 mL). A further portion of MeOH (5 mL) was then added, and the resulting solution was neutralized with a saturated solution of NH_3 in MeOH. The solvent was completely removed from the suspension obtained. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH, 99:1 to 95:5) to afford, after recrystallization from MeOH, **17** (45 mg, 68%) as white crystals; m.p. 251−253 °C. − IR (KBr): $\tilde{\nu}$ = 3324 cm^{-1}, 3139, 1668, 1608, 1571, 1486, 1330, 1099, 1070, 1024. − ^1H NMR ([D$_6$]DMSO): δ = 3.11 (m, 2 H, 1′-H and 5′-H), 3.33 (m, 1 H, 4′-H), 3.51 (dd, *J* = 9.2, 6.5 Hz, 1 H, 2′-H), 3.84 (m, 1 H, 4′′-H), 4.21 (m, 1 H, 2′′-H), 4.37 (dd, *J* = 7.0, 5.6 Hz, 1 H, 6′-H), 4.76 (ddd, *J* = 7.0, 7.0, 5.5 Hz, 1 H, 7′-H), 5.59 (d, *J* = 5.5 Hz, 1 H, OH), 7.22 (br. s, 2 H, NH_2), 8.14 (s, 1 H, 2-H or 8-H), 8.28 (s, 1 H, 2-H or 8-H). − ^{13}C NMR ([D$_6$]DMSO): δ = 40.0 (C-1′ or C-5′), 40.4 (C-1′ or C-5′), 60.0 (C-6′ or C-7′), 65.2 (C-6′ or C-7′), 67.0 (C-4′ or C-2′), 70.3 (C-4′ or C-2′), 119.1 (C-5), 140.0 (C-8), 149.6 (C-4), 152.3 (C-2), 156.0 (C-6). − HRMS ($C_{11}H_{14}N_5O_2$): calcd. 248.1147; found 248.1169 [M + H].

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