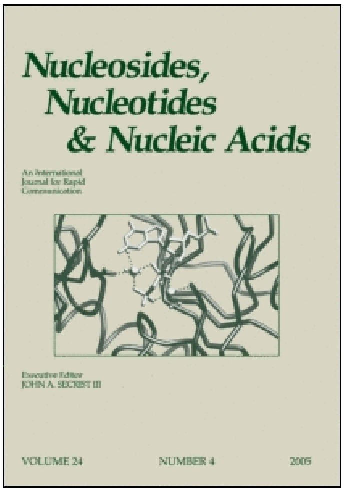

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STUDIES TOWARDS THE SYNTHESIS OF THE SATURATED AND UNSATURATED CARBOCYCLIC METHYLENE PHOSPHONATE ANALOGS OF DIDEOXYADENOSINE

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Abstract : The synthesis of the saturated carbocyclic methylene phosphonate analog of ddAMP is described by two different methods (epoxyde opening and "purinoselenylation"). Studies towards the formation of 2',3' unsaturated analogs by selenoxyde or mesylate elimination are also reported.

INTRODUCTION

The growing interest in the synthesis of nucleoside analogs is closely related to the successful use of this class of compounds as therapy in viral diseases. Considering HIV replication inhibitors, dideoxyinosine 1 (ddI) recently emerged[1] among all the purine nucleoside analog ever prepared since this compound is the second agent, after AZT, to be approved for the treatment of AIDS. The mechanism of action of ddI as an anti-retroviral agent has been extensively studied and it is generally admitted that ddI is intracellularly transformed into ddATP 3 which is a potent inhibitor of HIV reverse transcriptase[2]. 2',3'-Dideoxyadenosine monophosphate 2 (dd AMP) has been identified[3] as a key intermediate in that metabolic processes required for antiviral activity. However, ddI is also known to be metabolically unstable in vivo since the glycosidic bond of this nucleoside analog is rapidly hydrolyzed chemically at acidic pH[4] and rapidly phosphorolyzed enzymatically by purine nucleoside phosphorylase in human blood erythrocytes[5].

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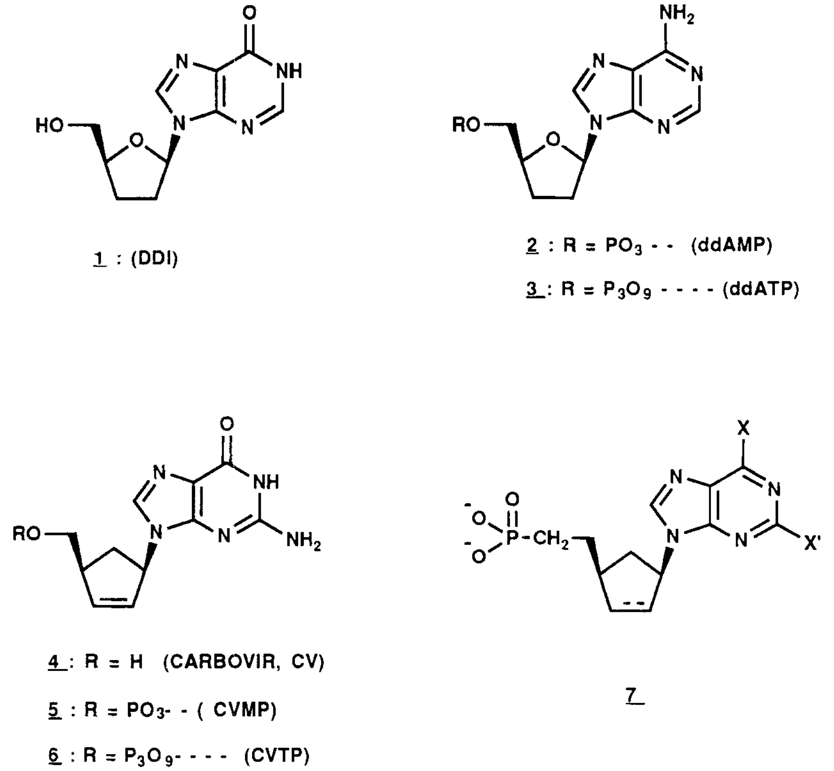


1 : (DDI)

2 : R = PO_3 - - (ddAMP)

3 : R = P_3O_9 - - - - (ddATP)

4 : R = H (CARBOVIR, CV)

5 : R = PO_3- - (CVMP)

6 : R = P_3O_9- - - - (CVTP)

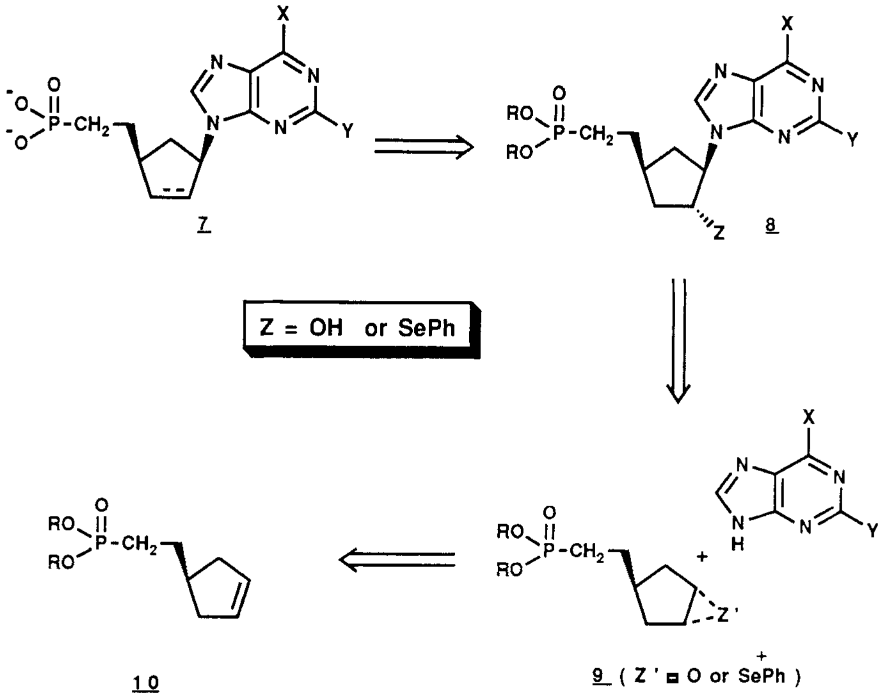
7

Scheme 1

To overcome these problems resulting from the lability of the glycosidic linkage, analogs of dideoxypurine nucleosides containing a fluorine atom in 2'-position[4b] or analogs where the oxygen atom in the sugar -derived moiety has been replaced by a methylene linker (i.e. carbocyclic nucleoside analogs) have been prepared and evaluated.

These studies resulted in the identification of carbovir 4, an unsaturated carbocyclic nucleoside which was found[6] to be a potent and selective inhibitor of HIV-1 replication in vitro. The mechanism of action of carbovir 4 is expected[7] to parallel that of dideoxy nucleoside analogs and this will require intracellular phosphorylation to the triphosphate 6 by host enzymes.

It has been demonstrated that CVTP 6 (like ddATP 3) is a potent Reverse transcriptase inhibitor[6c], but, unfortunately, carbovir 4 as well as ddI 1 are poorly transformed into their corresponding triphosphate derivatives 6 or 3 respectively in mammalian cells. This is mainly attributed to the fact that CV 4 and ddI 1 are very poorly phosphorylated into CVMP 5 or ddAMP 2, two key metabolites

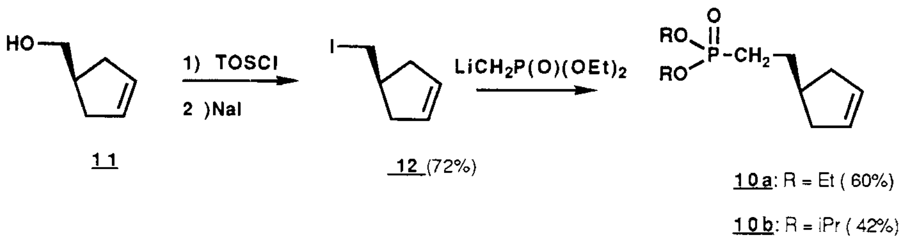


Scheme 2

required for antiviral activity[3]. This problem of poor phosphorylation of nucleoside analogs can be solved by designing nucleotide analogs, i.e. compounds in which a phosphonate group is mimicking the phosphate monoester. Examples[8] of such phosphonates of wide-spread current interest in the antiviral field are (S)-9-[3-hydroxy-2-(phosphono-methoxy)propyl]cytosine (HPMPC) and 9 [-2-(phosphono-methoxy)ethyl] adenine (PMEA). More recently, the synthesis of phosphonate derivatives of dideoxyribose has also been reported[9]. In this paper, we report our synthetic studies concerning the preparation of new analogs of ddAMP or CVMP of general formula 7 in which carbocyclic moiety (to avoid glycosidic lability) has been combined with a phosphonate functionality (to overcome the first phosphorylation step).

Results and discussion

The synthesis of carbocyclic nucleoside and analogs has been very well documented and several new methods have been described during the last few years[10,11]. Considering different synthetic approaches towards the carbocyclic derivatives 7, we concerned ourselves exclusively with convergent *methods*



Scheme 3

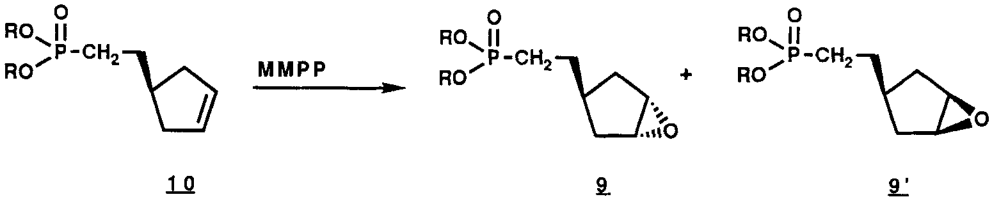
allowing the connection of the intact purine moiety with an electrophilic cyclopentyl derivative containing the desired phosphonate group. Because of the poor nucleophilicity of purine bases, the key step has been studied by starting from electrophilic cyclopentyl derivatives activated by 3-membered ring heterocycles such as the epoxydes or seleniraniums salts 9, both easily accessible from the corresponding cyclopentenyl derivatives 10 (scheme 2).

The success of the approach summarized in the retrosynthetic scheme 2 relies on two major points : first, the stereochemical control of the process requires that the oxirane or seleniranium salts intermediates 9 be preferentially formed on the less hindered face of the cyclopentane ring to direct the nucleophilic attack of the purine base on the same side than the phosphonate group. Secondly, the hydroxyl or selenophenyl groups in 8 must be easily and selectively transformed into the saturated and unsaturated 2',3' dideoxy carboxyclic nucleotide analogs 7. The requested cyclopentenyl phosphonates 10a (R=Et) and 10b (R=iPr) have been obtained from 1-hydroxy-methyl-3-cyclopentene 11[12] according to scheme 3.

The oxydation of the cyclopentenyl phosphonates 10a and 10b by using magnesium monoperoxyphtalate (MMPP) gives a 80/20 mixture of stereoisomeric epoxides (scheme 4) in which the cis isomers 9a or 9b have been identified as the major ones by ^{1}H NMR analysis.

All attempts to condense the anion of adenine with the epoxyde 9a failed to give the expected product 8a (Z=OH); the major product formed after reaction at 140°C in DMF for 20 hours was identified as 9-ethyladenine 13 (scheme 5) which is probably formed by a nucleophilic attack of the adenine anion on the phosphonate ethylester

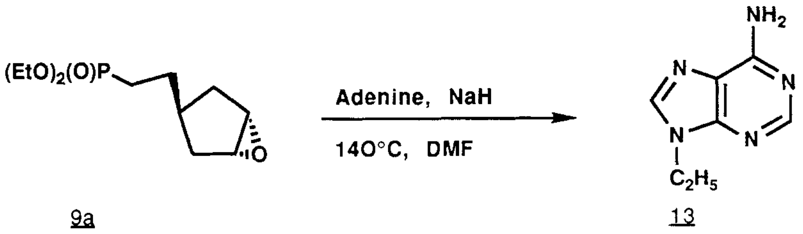
This problem could be solved by using the diisopropyl ester 9b (scheme 6) which, upon condensation with the sodium salt of adenine at 140°C in DMF was transformed into the expected product 8b (48% yield) together with 7% of the stereoisomer 8b' (scheme 7). The relative stereochemistry of the adducts 8b and



(a) : R = Et : 75%

(b) : R = iPr : 79%

Scheme 4

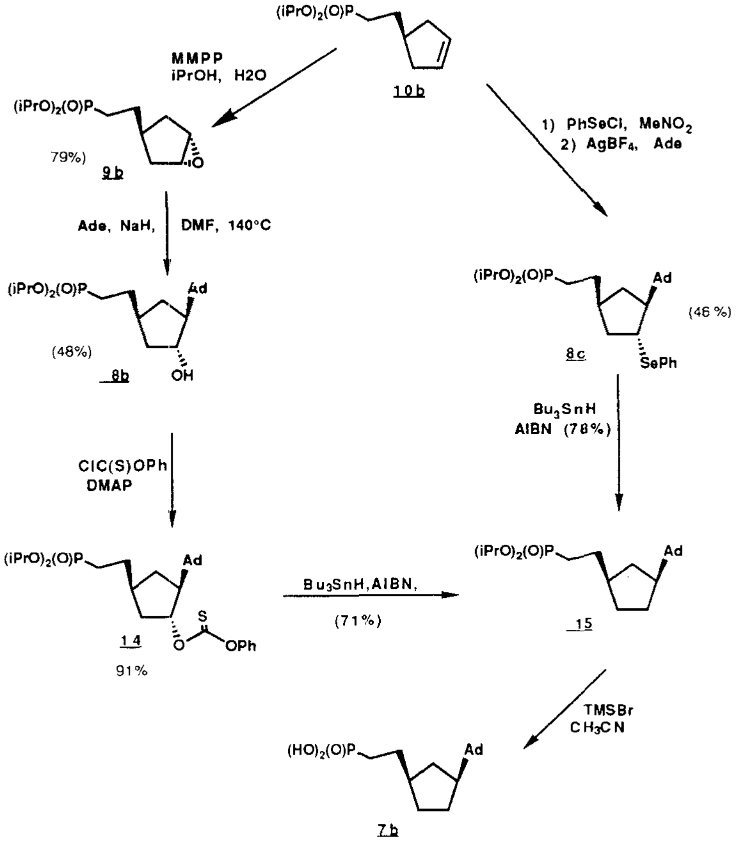


Scheme 5

8b' is explained by the use of the mixture of epoxydes 9b and 9b' and has been confirmed by ^{1}H NMR analysis (2D experiments). Moreover, only 7% of 9-isopropyl adenine were isolated under these conditions which represents a clear improvement when compared to the same reaction using the diethyl phosphonate 9a as starting material.

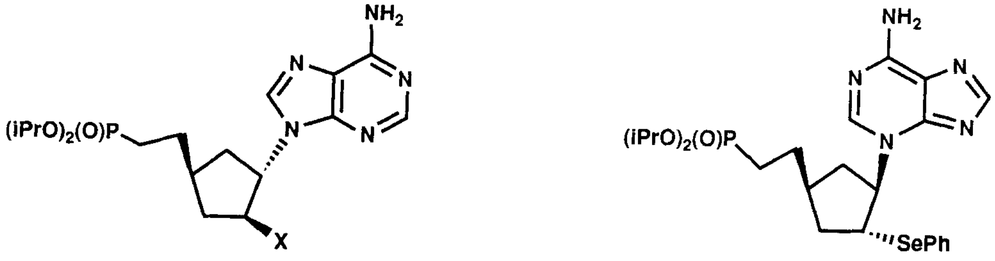
It is noteworthy that the formation of N-7 substituted adenine regioisomers was only marginal (< 3%) under these conditions as revealed by ^{1}H NMR and ^{13}C NMR analysis.

The formation of the saturated carbocyclic methylene phosphonate analog of ddAMP 7b from the alcohol 8b has been performed by using the method of Barton[13] for the reduction of secondary alcohols (scheme 6) : the alcohol 8b is first reacting with phenylchlorothionocarbonate to give the thionocarbonate 14 (91% yield) which is then reduced by reaction with tributyltinhydride in toluene in the presence of AIBN to give the protected phosphonate ester 15 in 71% yield. Removal of the isopropyl phosphonate esters with bromotrimethylsilane 14 in acetonitrile gave the final expected product 7b in 62 % yield.



Scheme 6

Alternatively, the preparation of 7b was also studied by using the "purino-selenylation" method recently developed in our laboratory[14] ; thus, reacting the cyclopentenyl derivative 10b with phenylselenenyl chloride and adenine in nitromethane in the presence of $AgBF_4$, under sonochemical activation (scheme 6) leads to the preferential formation of the β-adenoselenide 8c in 46% yield together with 5% of the stereoisomer 8'c (scheme 7) and less than 3% of the N-7 regio-isomer. The major side product (9% yield) isolated under these conditions was the N-3 isomer 17 (scheme 7). The structure of 17 was deducted by ^{13}C NMR analysis (see experimental) and also by a strong UV absorption at 275 nM which are typical for N-3 substituted adenines[19] and contrasts with the UV absorption observed at 260 nM for the N-9 regioisomer 8c. Reduction of the carbon-selenium bond of 8c with tributyltinhydride[15] allowed the direct formation of the diisopropyl ester 15 in 78% yield (scheme 6). Comparison of the two methods depicted in scheme 6



8b'

8b' : X = OH

8c' : X = SePh

17

Scheme 7

shows that the "purinoselenylation" approach allows the preparation of 15 in two steps from 10b with a global yield of 36% and a stereochemical control higher than 90 % while the epoxyde opening route requires 4 steps to go from 10b to 15 (24% global yield) and a stereochemical control of 84%. It is also noteworthy that the purinoselenylation method has also been successfully applied[14] to the diethylester 10a ; this contrasts with the epoxyde route which requires drastic conditions uncompatible with a phosphonate diethylester group.

Considering the preparation of 2',3'-unsaturated carbocyclic phosphonate analogs of nucleotides, we have first studied the selenoxyde fragmentation starting from the selenopurine derivative 8c. Although the syn elimination of nucleosidic 2'-selenoxydes has been shown[15] to regioselectively produce the 2',3' unsaturated derivative, in our case, the major elimination product coming from the oxydation of 8c was found to be the "1'-2'"* unsaturated carbocyclic phosphonate derivative 18b (scheme 8) together with some expected "2',3'"* unsaturated derivative 18a. The structures of 18a and 18b have been deducted from ^{1}H NMR.
Replacing adenine in substrate 8c by 6-chloropurine did not change the regiochemistry of the selenoxyde fragmentation.

These results, when compared to the regiochemistry observed in the nucleoside case, illustrates the well-known importance of oxygen in directing selenoxyde fragmentation but, also, indicate that a β-purine substituent favors the formation of the enamino derivative in such a process. This contrasts with the exclusive

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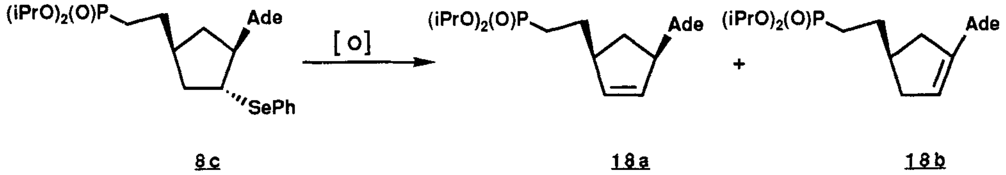
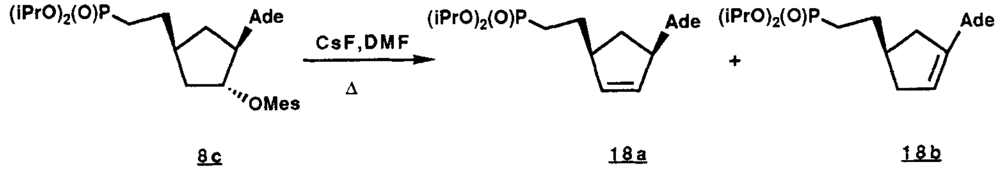
* This numbering of carbocycle carbon atoms is used by analogy with the numbering of nucleosides but differs from the correct nomenclature used in the experimental part.



$NaIO_4$, MeOH, H_2O : 18a /18b = 12/88

H_2O_2, THF : 18a / 18b = 18/82

Scheme 8



Scheme 9

formation of allylic amides observed[16] when β-selenoamides are oxidized with H_2O_2 but may be compared to the preferential formation of 1-nitroolefins by elimination of β-nitroselenoxydes[17].

In view of these disappointing results, we turned our attention towards the dehydration of the purino-alcohol 8b via an anti-elimination mechanism which should take place regioselectively between the 2' and 3' positions. Therefore, the alcohol 8b was transformed in the mesylate 19 (72 % yield) ; however all attemps to eliminate the mesylate using alkoxide or amine bases failed to give the expected 2',3' unsaturated derivative 18a. Fortunately, the preferential formation of 18a was observed when 19 was reacting with cesium fluoride in DMF[18] at 120°C (scheme 9). Under these conditions, 18a, was formed in 60 % yield together with 17 % of the 1'-2' unsaturated isomer 18b according to ^1H NMR analysis. Unfortunately, this side product 18b could not be separated from 18a by flash chromatography purification on silica gel.

In conclusion, the synthesis of the saturated and unsaturated carbocyclic methylene phosphonate derivatives of adenine has been described by two methods from the cyclopentenyl phosphonate 10b. Both epoxyde opening and purinoselenylation methods allow a good stereochemical control (> 85 %) and a very good regiochemical control (N9/N7 > 95/5) for the condensation of adenine with the cyclopentyl ring. The purinoselenylation route is particularly recommended for the preparation of the saturated derivative since the C-Se bond is easily reduced but the epoxyde opening method is prefered for the preparation of the 2',3' unsaturated analog because of the regiochemical control of the mesylate elimination.

Experimental Section

Reagents. All chemical reagents are from Janssen Chemica (Beerse, Belgium). They were used without further purification.

General Methods. Melting points were obtained on a Buchi SMP-20 melting point apparatus and are uncorrected. Proton and fluorine NMR spectra were recorded on either a Bruker spectrometer 200 MHz or 360 MHz. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS for ^{1}H NMR and from trifluoroacetic acid or hexafluorobenzene for ^{19}F NMR. Mass spectra were recorded on a Finnigan TSQ46 apparatus. Thin-layer chromatography was performed on silica gel 60F-254 plates (Merck ; 0.2-mm layer). Flash column chromatography utilized silica gel 60 as the solid phase (230-400 mesh) from E. Merck laboratories.

Synthesis of 1-Tosyloxymethyl-3-cyclopentene

A solution of p-toluenesulfonyl chloride (38.0 g ; 200 mmol) in 200 mL of dichloromethane is added dropwise to a solution of 1-hydroxymethyl-3-cyclopentene 11 (19.6 g ; 200 mmol), triethylamine (27.8 mL ; 200 mmol) and DMAP (0.24 g ; 2 mmol) in 200 mL of dichloromethane at -10°C under argon. The white suspension is vigourously stirred at 20°C for 18 hrs and filtrated ; the filtrate is concentrated under reduced pressure and the residue is purified by flash chromatography on silica gel (pet. ether/ether = 9/1) to give 38 g (75 % yield) of 1-tosyloxymethyl-3-cyclopentene after crystallisation from ether-petroleum ether
Rf = 0.3 (10% Ether-90% pet. ether)
MS : 253 (MH^+) ; 270 (MNH_4^+).
^{1}H NMR ($CDCl_3$) : 7.78 (d, 2H, arom.) ; 7.35 (d, 2H, arom.) ; 5.59 (m, 2H, vinyl) ; 3.92 (d, 2H, OCH_2) ; 2.45 (s, 3H, CH_3) ; 2.38-2.61 (m,3H, cycl.) ; 1.98-2.09 (m,2H, cycl.)
Anal. ($C_{13}H_{16}O_3S$) : calc. : C : 61.88 ; H : 6.39
found : C : 62,20 ; H : 6.41

Synthesis of 1-iodomethyl-3-cyclopentene (12)

Sodium iodide (33.3 g ; 222 mmol) is added to a stirred solution of 1-tosyloxymethyl-3-cyclopentene (55.98 g ; 222 mmol) in 200 mL of acetone and the reaction mixture is heated at 40°C for 6 hours under argon and filtrated. The filtrate is concentrated under reduced pressure and purified on silica gel by using petroleum ether to give 46.72 g of product after evaporation of the solvent under reduced pressure. The pure iodide 12 (41.6 g : 95 %) is finally obtained after distillation (75°C ; 15 mmHg).

Rf : 0.68 (30 % Ethyl acetate - 70 % pet. Ether))
MS : 209 (MH^+)
^{1}H NMR ($CDCl_3$) : 5.69 (m, 2H, vinyl) ; 3.25 (d, 2H , CH_2I) ; 2.45-2.67 (m, 3H cycl.) ; 2.02-2.17 (m, 2H, cycl).
Anal (C_6H_9I) : calc. : C : 34.64 ; H : 4.36
found : C : 34.67 ; H : 4.32

Synthesis of [3-cyclopenten-1-yl)ethyl]phosphonic acid, diisopropyl ester (10b)

A 1.63 N solution of n-butyllithium in hexane (100 mmol) is added dropwise to a stirred solution of diisopropyl methyl phosphonate (18 g, 100 mmol) in 100 mL of THF at -78°C under argon. After stirring for 1 hr, the iodide 12 (20.8 g, 100 mmol) is added dropwise at 0°C. The reaction mixture is stirred at 0°C for 18 hrs , quenched by adding excess saturated aqueous ammonium hydroxyde and concentrated under reduced pressure. The residue is dissolved in ether, washed with water and brine, dried over sodium sulfate, filtrated, evaporated and purified by flash chromatography on silica gel by using ethyl acetate as eluent to give 10.9 g (42 % yield) of product 10b.

Rf : 0.58 (10% MeOH$^-$ 90 % $CHCl_3$)
MS : 261 (MH^+) ; 28 (MNH_4^+)
^{1}H NMR ($CDCl_3$) : 5.65 (m, 2H, vinyl) ; 4.70 (m, 2H, CH ($(CH_3)_2$) 1,60-2.55 (m,9H, cycl + CH_2CH_2P) ; 1.31 (d, 12H,CH_3)
Anal. ($C_{13}H_{25}O_3P$) : calc : C : 59.88 ; H : 9.68
found : C : 59.83 ; H : 9,60

Synthesis of [2-(cyclopent[5]oxiran-4-yl)ethyl] phosphonic acid, diisopropyl ester (9b)

A solution of magnesium monoperoxyphtalate (8.72 g ; 17,6 mmol) in water (45 mL) is added dropwise to a stirred solution of the diisopropylester 10b (6.5 g : 25 mmol) in 30 mL of isopropanol at 20°C. After stirring for 5 hours at 20°C, the reaction mixture is quenched by addition of excess sodium thiosulfate and concentrated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water and brine, dried over sodium sulfate, filtrated, evaporated and purified by flash chromatography on silica gel (using ethyl acetate and increasing amounts of methanol as eluents) to give 5.42 g of epoxydes 9b and 9b' (79 % as a 80/20 mixture).

Rf : 0.65 (10 % MeOH - 90 % $CHCl_3$)
MS : 277 (MH^+) ; 294 (MNH_4^+)
^1H NMR ($CDCl_3$) : 4.67 (m, 2H, OCH) ; 3.47 (s, 2H, epox., minor isomer) ; 3.45 (s, 2H, epox., major isomer) ; 2.14-2.25 (m, 2H, cycl.) ; 1.56-1.89 (m, 5H , cycl. + $\underline{CH_2CH_2}P$) ; 1.32 (d, 12H, CH_3) ; 1.18-1.26 (m, 2H, cycl.).

Synthesis of [2-[3-(6-amino-9H-purin-9yl)-4-hydroxy-cyclopentyl]ethyl] phosphonic acid, diisopropylester (8b)

Adenine (3.57 g ; 26 mmol) is added portionwise to a stirred suspension of sodium hydride (1.23 g ; 31 mmol freshly washed with hexane) in 20 mL of DMF, at 20°C under argon. After stirring for 30 min, a solution of epoxyde 9b and 9b' (6.08 g ; 22 mmol) in 10 mL of DMF is added to the reaction mixture which is stirred at 140°C for 72 hours. DMF is evaporated under reduced pressure and the residue is purified by flash chromatography on silica gel by using chloroform and increasing amounts of methanol as eluents to give 3.18 g (56 % yield) of a 84/16 mixture of isomers (respectively 8b and 8b') as a white solid.
Rf : 0.10 (10 % MeOH - 90 % $CHCl_3$)
M p : 117°C
MS : 412 (MH^+) ; 295
^1H NMR (CD_3OD ; 500 MHz) : 8.32 (s,H2) ; 7.74 (s, H8) ; 6.29 (s, NH_2) ; 4.70 (m, 2H, $\underline{CH}(CH_3)_2$) 4.54 (m,1H, $\underline{CH}$-OH) ; 4.47 (m, 1H, $\underline{CH}$-N) ; 2.56 (m , 1H, cycl.) ; 2.36 (m, 1H cycl. and 1H, OH) ; 2.02 (m, 1H, cycl.) ; 1.90 (m, 1H, cycl.) ; 1.80 (m, 1H, cycl.) ; 1.66 (m, $\underline{CH_2CH_2}P$) ; 1.31 (d, 12H, OCH $(\underline{CH_3})_2$).
2D NMR (NOESY experiments) show interactions between cyclic H_1 (δ = 2,15) and $H_{2\alpha}$ (δ = 2,56), H_1 and H_3 (δ = 4,47), H_3 and $H_{2\alpha}$. This is in agreement with the fact that H_1 and H_3 are on the same side than $H_{2\alpha}$ and means that both phosphonate and adenine are in cis relationship.
The minor isomer is characterized by signals at 7.9 (purinyl H2), 8.21 (purinyl H8) and 6.62 (NH_2).

Anal. ($C_{18}H_{30}N_5O_4P$) :	calc : C : 52.55 ;	H : 7.35 ;	N : 17.02
	found : C : 52.19 ;	H : 7.43 ;	N : 16.76

IR (KBr) 3500-3000, 2982, 2932, 1651, 1607, 1244 cm^{-1}

Synthesis of [2-[3-(6-amino-9H-purin-9yl)-4-(phenyl thionocarbonate)-cyclopentyl]-ethyl] phosphonic acid diisopropylester (14).

Phenylthionocarbonate (2.0 mL ; 14.5 mmol) is added dropwise to a stirred solution of 8b (2.76 g ; 6.7 mmol) and DMAP (2.6 g ; 2.4 mmol) in 140 mL of anhydrous acetonitrile.

The reaction mixture is stirred at 20°C for 20 hours and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (eluents : chloroform and methanol) to give the expected product 14 (3.26 g ; 91% yield) as a 84/16 mixture of isomers.

Rf : 0.35 (10% MeOH - 90% $CHCl_3$)

MS : 548 (MH^+) ; 412 (MH^+-$SCOC_6H_5$)

^1H NMR (200 MHz, $CDCl_3$) : 7.84 (s, H8) ; 8.34 (s, H2), 7.01-7.41 (m,5H,C_6H_5) ; 6.00 (m, 1H, $CHOC(S)OC_6H_5$) ; 5.70 (s, NH_2) ; 5.01 (m, 1H, CHAde) ; 4.72 (m, 2H, $OC\underline{H}(CH_3)_2$) ; 2.13-2.48 (m,6H, cycl.) ; 1.7-1.82 (m, 4H, $\underline{CH_2CH_2}P$) ; 1.33 (d, 12H, CH_3).

Anal. ($C_{25}H_{34}N_5O_5PS$): calc. : C : 53.95 ; H : 6.34 ; N : 12.58
found : C : 53.76 ; H : 6.17 ; N : 12.73

Synthesis of [2-[3-(6amino-9H purin-9 yl) cyclopentyl]ethyl] phosphonic acid, diisopropyl ester (15) from (14).

AIBN (0.57 g ; 3.6 mmol) and tributyltinhydride (6.14 g ; 24 mmol) are added to a solution of the thionocarbonate 14 (3.20 g ; 5.9 mmol) in 170 mL of anhydrous toluene. The reaction mixture is stirred at 75°C for 6 hours and for 1 hr at 100°C, then concentrated under reduced pressure and the residue is purified by flash chromatography on silica gel by using increasing amounts of methanol in chloroform as eluents to give 2.07 g of product 15 (71 % yield) as a 84/16 mixture of isomers.

Rf : 0.25 (10 % MeOH-90 % $CHCl_3$)

MS : 396 (MH^+)

^1H NMR (200 MHz ; CDCl3) : 8.35 (s, H2) ; 7.88 (s, H8) ; 6.02 (s, NH_2) ; 4.92 (m, 1H, CHN) ; 4.72 (m, 2H, $\underline{CH}$ $(CH_3)_2$) ; 1.91-2.54 (m, 7H, cycl) ; 1.61 (m, 4H, $\underline{CH_2CH_2}P$) 1.42 (d, 12H, CH_3).

Synthesis of [2-[3-(6-amino-9H-purin-9-yl)cyclopentyl]ethyl]phosphonic acid (7b)

Trimethylsilylbromide (1.5 mL ; 11 mmol) is added dropwise to a stirred solution of 15 (1.5 g ; 3.8 mmol) in 15 mL of anhydrous acetonitrile at 20°C under argon. The white suspension is stirred at 20°C for 12 hours and acetonitrile is removed by evaporation under reduced pressure. The residual white solid is redissolved in acetonitrile and hydrolyzed by addition of 0.5 mL of water. After evaporation, the product is crystallised from water to give 0.757 g (67 % yield) of 7b as a 84/16 mixture of isomers.

MS (FAB) : 312 (MH^+) ; 404 ($MglyH^+$)

^1H NMR (NaOD, D_2O ; 360 MHz) : 8.25 (s, H2) ; 8.10 (s, H8) ; 4.70 (dt, 1H, CHN) ; 2.42 (m, 1H, cycl.) ; 2,19 (m, 1H, cycl.) ; 1.98 (m, 1H, cycl) ; 1.82 (m, 1H, cycl.) ; 1.39 -1.68 (m, 1H cycl., 4H, $\underline{CH_2CH_2}P$).

^{13}C NMR (D_2O, NaOD ; 360 MHz) : 29.69 (d, CH_2P ; JC-P = 129.5 Hz) ; 30.83, 31.82 ; 32.74 ; 40.06 ; 40.75 ; 57.06 ; 119.72 ; 141.57 ; 149.86 ; 153.50 ; 156.50.

Anal ($C_{12}H_{18}N_5O_3P$; 0.2 H_2O): calc. : C : 45.77 ; H : 5.84 ; N : 22.24
found : C : 45.51; H : 5.67 ; N : 21.93

Synthesis of [2-[3-(6-amino-9H-purin-9-yl)-4-(methanesulfonyloxy)-cyclopentyl]ethyl]phosphonic acid, diisopropyl ester (19)

Mesyl choride (0.59 mL ; 7.5 mmol) is added dropwise to a stirred solution of the alcohol 8b (2.06 g ; 5 mmol) and triethylamine (1.09 g ; 7.8 mmol) in 20 mL of anhydrous dichloromethane at 0°C under argon.

The reaction mixture is stirred at 20°C for 3 hours, evaporated under reduced pressure and purified by flash chromatography on silica gel (by using ethyl acetate and increasing amounts of methanol as eluents) to give the mesylate derivative 19 in 72 % yield (1.75 g) as a white solid (m.p. : 61°C).

MS ($C_{19}H_{32}N_5O_6P$) : 490 (MH^+) ; 394 (MH^+-OSO_2CH_3)

^1H NMR (200 MHz ; CDCl3) :

8.34 (s,H2) ; 7.84 (s, H8) ; 7.01-7.41 (m, 5H, arom.) 5.86 (s, NH_2) ; 5.58 (s, 1H, CHOMs) ; 4.84 (m, 1H, CH Ade) 4.72 (m, 2H, OCH(Me)$_2$) ; 2.85 (s, 3H,CH_3SO_3) ; 2.05-2.45 (m,5H, cycl.) ; 1.72 (m, 4H, CH_2CH_2P) ; 1.3 (d, 12 H, OCH (Me)$_2$).

IR (KBr) 3422, 2981, 2935, 1647, 1600, 1356, 1177, 1244 cm^{-1}

Anal. ($C_{19}H_{32}N_5O_6P$, 0.5 H_2O) :
calc. : C : 45.78 ; H : 6.67 ; N : 14.05
found : C : 45.53 ; H : 6.52 ; N : 14.08

Synthesis of [2-[3-(6-amino-9H purin-9yl)-4-phenylseleno-cyclopentyl]ethyl]phosphonic acid, diisopropyl ester (8c)

A solution of phosphonate 10b (0.65 g ; 2.5 mmol) and phenylselenenyl chloride (0.48 g ; 2.5 mmol) in 5 mL of nitromethane is sonicated for 30'. Adenine (0.68 g ; 5 mmol) and silver tetrafluoroborate (0.49 g ; 2.5 mmol) are added to the reaction mixture which is stirred under sonication for 6 hours and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel to give 0.66 g (49 %) of expected product 8c (containing 4% of the stereoisomer 8c'), and 100 mg of the N-3 regioisomer 17.

8c : Rf : 0.64 (90 % CHCl3 - 10 % MeOH)

UV (4.67.10-5 M/MeOH) (λmax/ξ) : (199.0/41260) ; (259.80/20085)

MS : 552 (MH^+) ; 396 (MH^+-Seϕ) ; 262 (MH^+-Seϕ-Ade) 136 (Ad^+).

^1H NMR ($CDCl_3$; 360 MHz) : 8.21 (s, H2) ; 7.53 (s, H8) 7.02-7.33 (m, 5H, arom.) ; 6,32 (s,2H, NH_2) ; 4.63 (m, 1H, CHN) ; 4.18 (m, 1H, CHSe) ; 2,27 (m, 1H, cycl.); 2.12

(m, 2H, OCH_2) ; 2.02 (m, 2H, cycl.) 1.76 (m, 2H, cycl.) ; 1,63-1,68 (m, 2H, CH_2P) ; 1,27 (d, 12H , CH $(CH_3)_2$)

2D NMR (NOESY experiments) show interactions between cyclic H1 (δ = 2,15) and H2α (δ = 2,00), H1 and H3 (δ = 4,63), H3 and H2α. This is in agreement with the fact that H_1 and H_3 are on the same side than H_2 and means that both phosphonate and adenine are in cis relationship.

17 : Rf : 0.31 (85 % $CHCl_3$ - 15 % MeOH)

MS : 552 (MH^+) ; 284 ; 261 ; 154 ($AdeH^+$)

UV : ($9,45.10^{-5}$ M/MeOH) (λ max/ξ) : (193.9/61950) ; (209.3/43080) ; (275.2/17410).

^1H NMR (CD_3OD ; 360 MHz) : 7.14 (t, 2H, arom.) ; 7.03 (t, 1H, arom) ; 6.89 (t, 2H, arom.) ; 4.86 (m, 1H, CHAde) ; 4.52-4.62 (m, 2H, CH $(CH_3)_2$, 1H, CHSeϕ) ; 2.20-2.27 (m, 5H, cycl.); 1.75-1.81 (m,4H,$O(CH_2)_2P$) ; 1.40 (d, 12H, $CH(CH_3)_2$)

^{13}C NMR : 156.3 (C6, Ade) ; 152.5 (C8, Ade) ; 149.7 (C4, Ade) ; 144.6 (C2, Ade) ; 121.3 (C5, Ade) ; 135.4 (CH, Arom.) ; 129.6 (CH, Arom.) ; 128.5 (CH, Arom.) ; 128.5 (C, Arom.); 73.06 (CH, Ade) ; 72.08 (CH(iPr)) ; 44.90 (CH Seϕ) ; 37.85 (CH_2, cycl.) ; 37.53 (CH cycl.) ; 36.98 (CH_2cycl.) ; 29.61 (CH_2O) ; 25.35 (CH_2P) ; 24.29 (CH_3).

Synthesis of [2-[3-(6 amino-9H purin-9yl)cyclopentyl]phosphonic acid, diisopropyl ester (15) from (8c) :

Tributyltin hydride (0.56 mL ; 2 mmol) and AIBN (10 mg) are added to a solution of 8c (552 mg, 1 mmol) in 30 mL of anhydrous toluene. The reaction mixture is stirred at 75°C for 3 hours, evaporated under reduced pressure and purified by flash chromatography on silica gel (using chloroform and methanol (95/5) as eluents) to give 0.31 g (78% yield) of a colorless oil corresponding to a 9/1 mixture of stereoisomers. Spectral data are identical to those described previously.

Oxidation of 8c and selenoxide fragmentation

Method A ($NaIO_4$) :

Sodium metaperiodate (2.5 mmol ; 0.52 g) is added to a stirred suspension of the selenide 8c (0.9 g ; 1.6 mmole) in 20 mL of a 9:1 mixture of methanol and water. The reaction mixture is stired at 20°C for 5 hours ; methanol is evaporated under reduced pressure and the resulting aqueous suspension is extracted with ethylacetate. The crude reaction mixture obtained after ethylacetate evaporation has been identified as 92/18 mixture of 18b and 18a respectively by 1H NMR analysis : 18b is characterized by a vinylic proton at 6.45 ppm while 18a is characterized by $H_{1'}$ (m, 6.25 ppm) ; $H_{2'}$ (m, 5.75 ppm) and $H_{3'}$ (m, 5.95 ppm).

MS : 394 (MH^+)

Method B (H_2O_2)

Hydrogen peroxide (0.9 mL of a 30 % solution in water) is added to a stirred solution of 8c (2.5 mmol ; 0.9 g) in 7 mL of THF at 6°C. After stirring at 6°C for 2h30 and a 18°C for 30 min., water is added and the mixture is extracted with dichloromethane. The crude reaction mixture obtained after dichloromethane evaporation has been identified as a 88/12 mixture of 18b and 18a respectively by ^{1}HNMR analysis (see Method A)

Synthesis of [2-[3-(6-amino-9H-purin-9yl)-2-cyclopenten-1-yl]ethyl]phosphonic acid, diisopropylester (18a) :

Cesium fluoride (0.75 g ; 6 mmol) is added to a stirred solution of mesylate 19 (0.79 g ; 1,6 mmol) in 12 mL of DMF at 120°C under argon. The reaction mixture is stirred at 120°C for 6 hours, evaporated under reduced pressure and purified by flash chromatography on silica gel to give a mixture of the cyclo-pentenyl derivatives 18a (60 %) and 18b (17 %).

18a is characterized in ^{1}H NMR spectroscopy by signals at 6.25 (m, $H_{1'}$) ; 5.95 (m, $H_{3'}$) and 5.75 (m, $H_{2'}$).

18b is characterized in ^{1}H NMR spectroscopy by a signal at 6.45 (m, vinyl H).

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