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Research paper

Synthesis of 3′-halo-5′-norcarbocyclic nucleoside phosphonates as potent anti-HIV agents

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Dedicated to Dr. Gilles Gosselin at the occasion of his retirement and his outstanding career in the field of nucleoside analogues as antiviral agents

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ABSTRACT

The synthesis and the antiviral evaluation of 3'-halo (iodo and fluoro) 5'-norcarbocyclic nucleoside phosphonates is described. No antiviral activity was observed against Zika virus, Dengue virus 2, HSV-1, HSV-2 and Chikungunya virus. In contrast, some of the synthesized compounds are potent inhibitors of the replication of HIV-1, comparatively to (*R*)-PMPA, with no concomitant cytotoxicity.

1. Introduction

More than three decades after the discovery of the Human Immunodeficiency Virus (HIV) as the etiologic agent of AIDS, there is no vaccine available for the prevention of AIDS and drugs are the only arsenal to treat HIV infections [1,2]. However, current treatments do not allow the eradication of the virus but contain its replication at undetectable level with the obligation for the infected individuals to stay on treatment for life. This is a crucial issue because all existing *anti*-HIV drugs have long-term side effects and may be associated with the rapid emergence of resistant viral strains in case of faulty observance to treatment or suboptimal treatment. These concerns still promote the research for novel molecular-based *anti*-HIV drugs. Among these later, nucleoside and nucleotide analogues are an important class of *anti*-HIV drugs [3] as illustrated with the clinical use of Abacavir, a carbocyclic nucleoside analogue, and Tenofovir disoproxil fumarate (TDF), the corresponding carbonate prodrug of (*R*)-9-(2-phosphonylmethoxypropyl)adenine (*R*-PMPA, Tenofovir), an acyclonucleoside phosphonate (Fig. 1).

In the case of carbocyclic nucleosides, such as Abacavir, the replacement of the endocyclic oxygen of the furanose ring by a methylene group confers chemical and metabolic stabilities. In the case of nucleoside phosphonates, such as Tenofovir, the presence of P-C bond instead of the hydrolysable P-O brings about a metabolic stability of the linkage with the phosphate moiety. As a part of our research on 5′-norcarbocyclic nucleoside phosphonates as potential anti-viral agents [4], we describe here the synthesis and the antiviral evaluation of their 3′-halo (iodo and fluoro) corresponding counterparts bearing purine bases.

2. Results and discussion

2.1. Chemistry

The strategy for the synthesis of 3′-halo-5′-norcarbocyclic nucleoside phosphonates was based upon the preparation of compound (±) **6** as a common precursor (Scheme 1). Furfuryl alcohol was used as starting material and provided carbocycle (±) **1**

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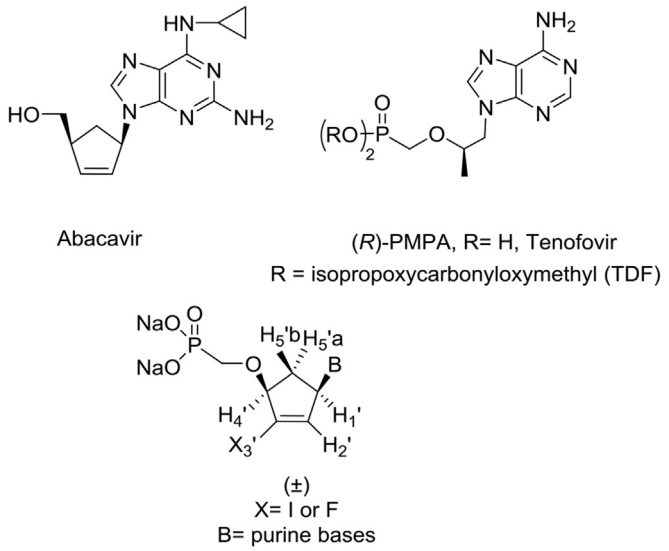


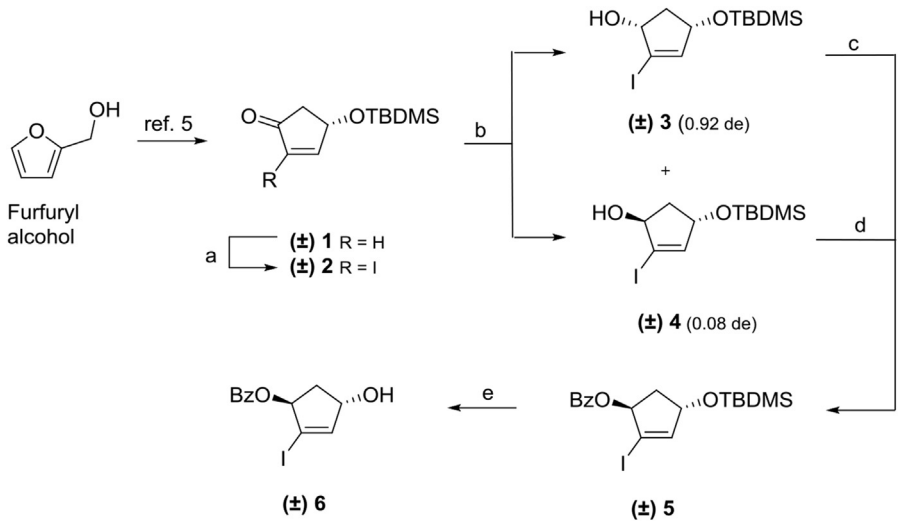
Fig. 1. Examples of *anti*-HIV carbocyclic nucleosides and acyclonucleoside phosphonates. Structures and numbering of the target 5′-norcarbonucleoside phosphonate analogues.

according to the procedure described by Curran [5]. The iodination reaction on compound (±) **1** was attempted according to the procedure described by Johnson (2 eq. of iodine in pyridine/CCl_4) [6,7]. Nevertheless, the moderate yield obtained (61%) prompted us to achieve the iodination reaction in the presence of pyridinium dichromate as a catalyst [8] and afforded α-iodinated enone (±) **2** in 86% yield. Reduction of the ketone under Luche conditions [9,10] gave a mixture of diastereoisomers (±) **3** and (±) **4**. These compounds were easily separated by purification on silica gel column chromatography and the diastereoisomers (±) **3** and (±) **4** (92/8 ratio) were isolated in 93% yield. From (±) **3**, a Mitsunobu reaction [11] in the presence of benzoic acid, PPh_3, and DIAD or a direct benzoylation of (±) **4** provided carbocyclic (±) **5** in 98% and 75% yield, respectively. Finally, the removal of the TBDMS protecting group in the presence of TBAF afforded the desired common precursor (±) **6** in 95% yield.

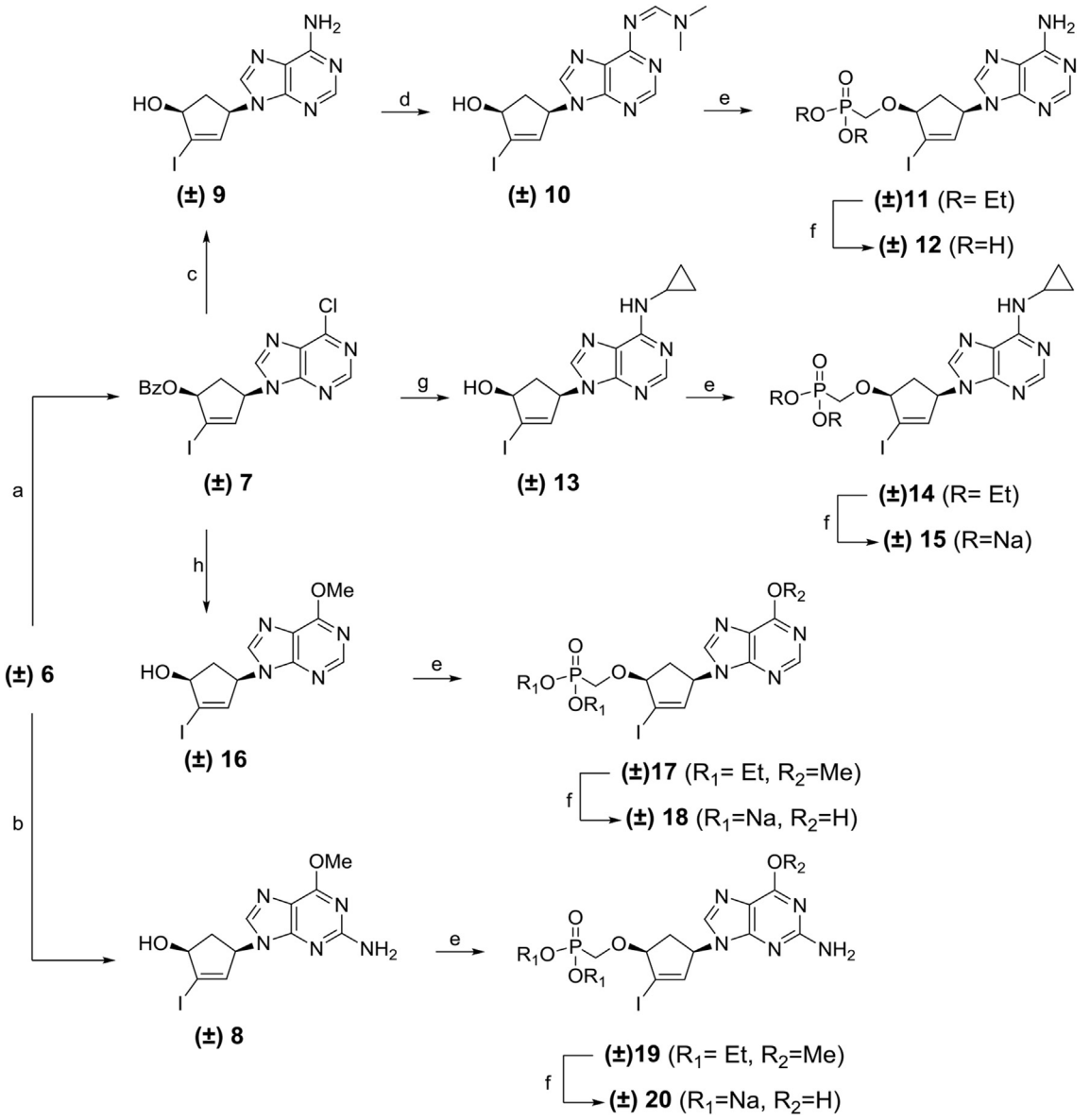
Synthesis of 3′-iodo-5′-norcarbocyclic nucleoside phosphonates bearing adenine, *N*-cyclopropyl-6-aminopurine, hypoxanthine and guanine (respectively compounds (±) **12**, (±) (**15**), (±) **18** and (±) (**20**) is described in Scheme 2.

Starting with a Mitsunobu coupling reaction between alcohol (±) **6** and an appropriate heterocyclic base, the *N9*-carbocyclic nucleosides were obtained without concomitant formation of the *N7* regioisomer [12]. Compound (±) **7**, a common intermediate for the synthesis of the target compounds (±) **12**, (±) (**15**) and (±) **18**, was obtained using 6-chloropurine as heterocyclic base whereas 2-amino-6-chloropurine was used to provide carbocyclic nucleoside (±) **8**, precursor of the target compound (±) **20**. The stereochemical assignments of compound (±) **7** were achieved through NMR experiments (Fig. 2). A NOE correlation between protons H1′ and H4′ was observed and support the *cis* orientation of these protons. These data were in agreement with our previous results on 3′-methyl-5′-norcarbocyclic nucleoside phosphonates [4] and confirm the stereochemistry obtained under Mitsunobu reaction.

Treatment of compound (±) **7** in the presence of methanolic ammonia gave the adenine derivative (±) **9** in 81% yield. Protection of the amino group as a *N,N*-dimethylformamidine [13] in order to avoid competing N-alkylation led to compound (±) **10** in 93% yield. *O*-Alkylation of (±) **10** in the presence of Li*Ot*Bu and diethyl *p*-toluene sulfonyloxymethyl phosphonate [14], followed by an acidic treatment, afforded carbocyclic nucleoside (±) **11** in 73% yield. Finally, the target nucleotide (±) **11** was obtained in 73% yield by deprotection of the phosphonate group in the presence of TMSBr in DMF. Concomitantly, nucleophilic substitution of compound (±) **7** with cyclopropylamine followed by removal of the benzoate group under basic conditions led readily to nucleoside (±) **13**. Condensation of the phosphonate group with carbocycle (±) **13** followed by the hydrolysis of the diethyl phosphonate esters was performed using as previously for (±) **12**. The phosphonic acid was then subject to an ion exchange chromatography to yield the target 3′-iodo-5′-norcarbocyclic nucleoside phosphonate (±) **15** as sodium salt. Then, we planned the synthesis of the derivative (±) **18** bearing hypoxanthine as nucleobase. In this respect, treatment of (±) **7** with potassium carbonate in methanol allowed the nucleophilic substitution of the chlorine atom and hydrolysis of the benzoate group to afford carbocyclic nucleoside (±) **16** in good yield. Condensation of the phosphonate group led to compound (±) **17** and removal of the diethyl phospho esters accompanied by the concomitant hydrolysis of the methoxy group in position 6 [4] gave the target



Scheme 1. Synthesis of carbocycle (±) **6**. Reagents and conditions: (a) I_2, PDC, CH_2Cl_2, rt, 46 h, 86%; (b) $CeCl_3$, $NaBH_4$, CH_3OH, −78 °C, 2 h, 93%; (c) benzoic acid, PPh_3, DIAD, THF, 0 °C, 1 h, 98%; (d) BzCl, pyridine/CH_2Cl_2, CH_2Cl_2, rt, 12 h, 75%; (e) TBAF, THF, 0 °C, 2 h, 95%.



Scheme 2. Synthesis of 3′-iodo-5′norcarbocyclic nucleoside phosphonates (±) **12**, (±) **15**, (±) **18** and (±) **20**. Reagents and conditions: (a) 6-chloropurine, DIAD, PPh_3, THF, rt, 2 h, 43%; (b) i) 2-amino-6-chloropurine, DIAD, PPh_3, THF, rt, 12 h; ii) K_2CO_3, MeOH, rt, 12 h, 44% over two steps; (c) methanolic ammonia, 70 °C, 20 h, 81%; (d) *N*,*N*-dimethylformamide dimethyl acetal, DMF, 50 °C, 4 h, 93%; (e) $(EtO)_2P(O)CH_2OTs$, Li*O*t*B*u, THF, for (±) **11**: 30 °C, 2 days, 73%; for (±) **14**, rt, 4 days, 76%; for (±) **17**: rt, 8 days, 67%; for (±) **19**: rt, 2 days, 53%; (f) TMSBr, DMF, rt; for (±) **12**, 12 h, 67%; for (±) **15**, 12 h, 69%; for (±) **18**, 30 h, 72%; for (±) **20**, 30 h, 58%; (g) i) cyclopropylamine, THF, 50 °C, 4 h; ii) K_2CO_3, MeOH, rt, 2 h, 85% over two steps; (h) K_2CO_3, MeOH, rt, 15 h, 75%.

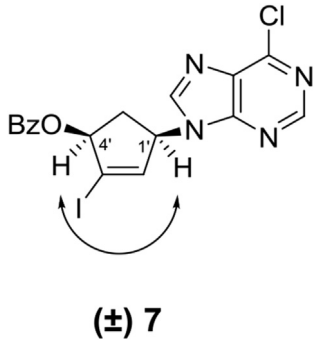
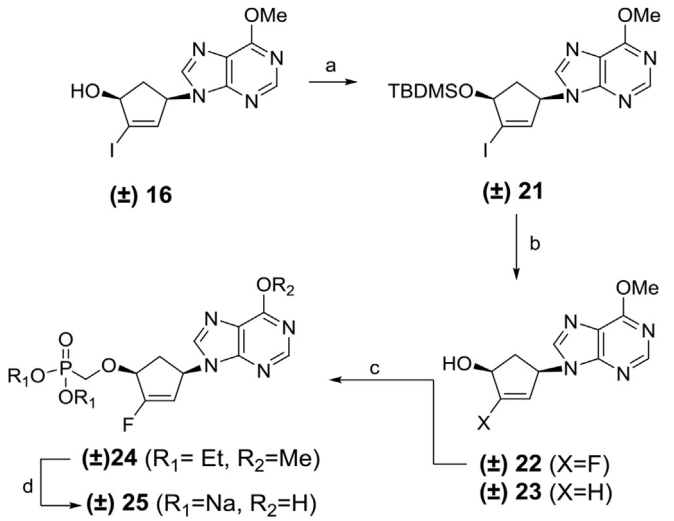


Fig. 2. Selected NOE effects on carbocyclic nucleoside (±) **7**.

compound (±) **18** in 72% yield, after purification by reversed-phase column chromatography and ion exchange on a dowex resin. The target compound (±) **20** was obtained from (±) **8** using similar procedure as described for compound (±) **18** from (±) **16**. The synthesis of the 3′-fluoro-5′-norcarbocyclic nucleoside phosphonates was first envisioned from a fluorination reaction on the 3′-iodo-5′-norcarbocyclic nucleosides previously obtained. Owing to the strongly basic conditions used in the fluorination step, this step has to be performed before the introduction of the phosphonate moiety. So, we first applied the strategy to the 3′-iodo-5′-norcarbocyclic nucleoside (±) **16** (Scheme 3). Since the fluorination step is carried out in the presence of *n*-BuLi, preliminary protection of the allylic alcohol as a silyl ether was required. The resulting compound (±) **21** was then submitted to an electrophilic fluorination in the



Scheme 3. Synthesis of 3′-fluoro-5′-norcarbocyclic nucleoside phosphonate (±) **25**. Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt, 12 h, 87%; (b) i) NFSI, *n*-BuLi, THF, −78 °C, 45 min; ii) TBAF, THF, 0 °C, 1 h, 21% over two steps for (±) **22**, 33% over two steps for (±) **23**; (c) $(Et_2O)P(O)CH_2OTs$, LiO*t*Bu, THF, rt, 12 days, 88%; (d) TMSBr, DMF, rt, 36 h, 70%.

presence of *n*-BuLi and NFSI [15] and led to an inseparable mixture of the desired 3′-fluoro-carbocyclic nucleoside and its unsaturated dehalogenated counterpart. Removal of the silyl ether was directly performed on the mixture, providing after purification by chromatography on silica gel compounds (±) **22** and (±) **23** in 21% and 33% yield, respectively from derivative (±) **21**. Condensation of the phosphonate group with the 3′-fluoro-carbocyclic nucleoside (±) **22** led to compound (±) **24**. Simultaneous deprotection of the phosphonate group and the base in the presence of TMSBr in DMF provided the 3′-fluoro-5′-norcarbocyclic nucleoside phosphonate (±) **25** in 70% yield.

Due to low yields and side-products obtained during the preparation of the fluoro derivative (±) **25**, we envisioned to carry out the fluorination step before the introduction of the heterocyclic base *via* the Mitsunobu reaction. In a first attempt, this approach was envisaged from *trans*-alcohol (±) **4** (Scheme 4, pathway 1). Nevertheless, the Mitsunobu reaction applied to the *trans* compound gave very poor yield (16%, data not shown), probably due to steric hindrance, generated between silyl ether and heterocyclic base as incoming nucleophile, during the S_N2 step occurring under Mitsunobu mechanism. Consequently, the *cis*-iodocarbocycle (±) **3** was used as starting material as implemented in Scheme 4 (pathway 2). A preliminary protection of the allylic alcohol before the fluorination step was accomplished to give the *tert*-butyldiphenylsilyl ether (±) **26**. Fluorination reaction was achieved in the presence of *n*-BuLi and NFSI leading to a mixture of carbocycles (±) **27** and (±) **28**. Under these conditions, the fluoro derivative was obtained as the major compound (*ratio* (±) **27**/(±) **28**: 7/3) as determined by ^1H NMR. However these compounds were very difficult to separate by chromatography on silica gel. Then, the selective hydrolysis of the *tert*-butyldimethylsilyl ether was performed under mild acidic conditions on the mixture to give the fluorinated carbocycle (±) **29** and its unsaturated counterpart (±) **30**. At this stage of the synthesis, these two compounds can be easily separated by chromatography on silica gel to obtain 57% of compound (±) **29** and only 22% of dehalogenated counterpart (±) **30**. As expected, this approach greatly improved the yield of the desired fluorinated product (±) **29** which was engaged in the Mitsunobu coupling reaction with different heterocyclic bases.

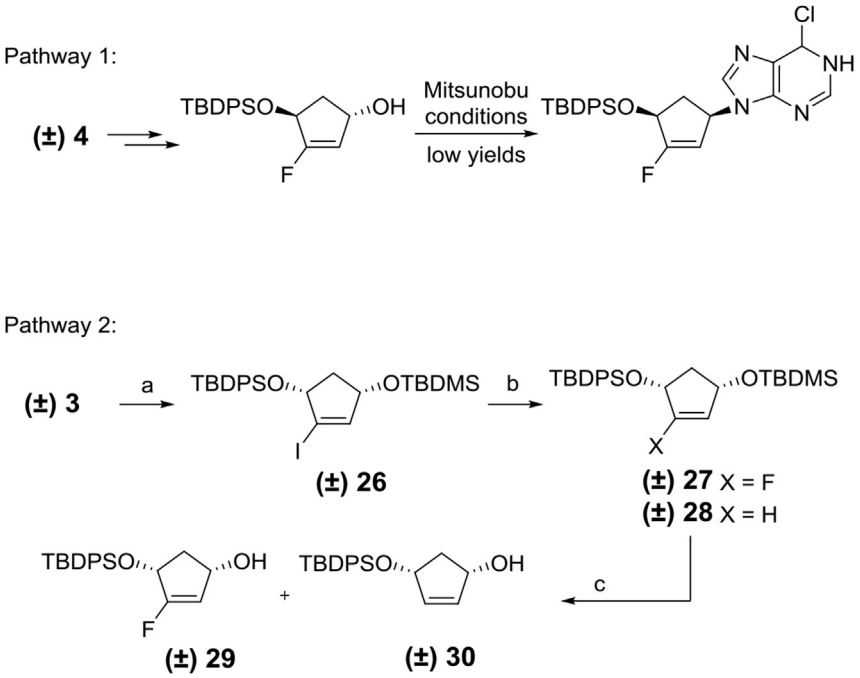
The syntheses of 3′-fluoro-5′-norcarbocyclic nucleoside phosphonates bearing adenine and guanine are reported in Scheme 5. Condensation of the fluorocarbocycle (±) **29** with 6-chloropurine or 2-amino-6-chloropurine was performed according to a Mitsunobu coupling reaction and led to the carbocyclic nucleoside derivatives (±) **31** and (±) **32** respectively, without concomitant formation of the *N7*-regioisomers. From compound (±) **31**, the desired carbonucleoside (±) **33** was obtained using a two steps procedure: the nucleophilic substitution of the chlorine atom in the presence of methanolic ammonia at 70 °C accompanied by a concomitant hydrolysis of the silyl ether, followed by the protection of the exocyclic amino function as *N*,*N*-dimethylformamidine group. Then, the inversion of the C4′-configuration was achieved using standard Mitsunobu protocol in the presence of benzoic acid, triphenylphosphine and DIAD in anhydrous THF and followed by the removal of the resulting benzoate group with K_2CO_3 in methanol to afford the carbonucleoside (±) **34**. This intermediate was converted into the corresponding phosphonate (±) **35** using a similar procedure as described for (±) **11**. Finally, the desired 3′-fluoro-5′-norcarbocyclic nucleoside phosphonate bearing adenine was obtained, as sodium salt, after deprotection of the phosphonate group with TMSBr in anhydrous DMF at room temperature and purification by reverse phase column chromatography and ion exchange chromatography. The target guanine derivative (±) **39** was obtained from compound (±) **32** following a nucleophilic substitution of the chlorine atom in the presence of potassium carbonate in refluxing methanol with the concomitant hydrolysis of the silyl ether to give compound (±) **37** in 80% yield. Inversion of the C4′-configuration on compound (±) **37** was achieved using similar protocol developed for (±) **34**. Finally, intermediate (±) **38** was successively converted into the phosphonate (±) **39** using a similar procedure as described for compound (±) **20**.

The stereochemical assignments of compounds (±) **36** and (±) **39** were achieved through NMR experiments (Fig. 3). In the case of compound (±) **36**, a NOE correlation was observed between H5′b and H8. Simultaneously, H5′a showed a correlation between protons H1′ and H4'. All these NOE correlations support the *cis* orientation of protons H5′a, H1′ and H4'. In the case of compound (±) **39**, a direct correlation between protons H1′ and H4′ was observed and gave proof of the *cis* orientation of protons H1′ and H4'.

2.2. Anti-HIV evaluation

The synthesized compounds (±) **12**, (±) (**15**), (±) **18**, (±) **20**, (±) (**36**) and (±) **39** were evaluated for their antiviral activity in human peripheral blood mononuclear cells (PBMC) infected with HIV-1. The results are summarized in Table 1. (*R*)-PMPA was used as positive control. Among the tested compounds, the 3′-iodo-5′-norcabonucleoside phosphonate (±) **12**, bearing adenine as nucleobase, exhibited moderate antiviral activity ($EC_{50} = 5.9$ μM). Modification of the adenine moiety by the introduction of a cyclopropyl group in position 6, as in compound (±) (**15**), resulted in the loss of activity. Replacement of the halogen atom in position 3′, as for 3′-fluoro-5′-norcabonucleoside phosphonate (±) **36** derivative of adenine afforded a compound with potent antiviral activity ($EC_{50} = 0.88$ μM) comparatively to (*R*)-PMPA ($EC_{50} = 1.1$ μM).

The others 3′-iodo or fluoro-5′-norcabonucleoside phosphonate bearing a purine base distinct of adenine did not display any antiviral activity against HIV-1. No concomitant cytotoxicity for all the target compounds was observed in PBM cells. The synthesized compounds (±) **12**, (±) (**15**), (±) **18**, (±) **20**, (±) (**36**) and (±) **39** were also evaluated for their antiviral activity against Zika virus, Dengue virus 2, HSV-1, HSV-2 and Chikungunya virus but did not show any antiviral activity (data not shown).



Scheme 4. Synthesis of the fluoro-carbocycle (±) **29**. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, rt, 2 days, 98%; (b) NFSI, *n*-BuLi, THF, −78 °C, 2 h; (c) TsOH, MeOH, rt, 1 h, 57% over two steps for (±) **29**, 22% over two steps for (±) **30**.

3. Conclusion

The racemic synthesis of 3′-iodo and 3′-fluoro-5′-norcarbocyclic nucleoside phosphonates bearing purine bases was undertaken and compounds were evaluated for their antiviral activity. No antiviral activity was observed against Zika virus, Dengue virus 2, HSV-1, HSV-2 and Chikungunya virus. In contrast, the 3′-iodo and 3′-fluoro-5′-norcarbocyclic nucleoside phosphonates bearing adenine as nucleobase, compound (±) **12** and (±) (**36**), exhibited anti HIV-1 with no concomitant cytotoxicity. Remarkably, The 3′-fluoro-5′-norcabonucleoside phosphonate (±) **36** exhibited significant antiviral activity, comparatively to (*R*)-PMPA. These interesting results warranty further studies, such as the synthesis of the suitable corresponding prodrugs, on 3′-fluoro-5′-norcarbocyclic nucleoside phosphonates as potential *anti*-HIV agents [16].

4. Experimental part

4.1. Chemistry

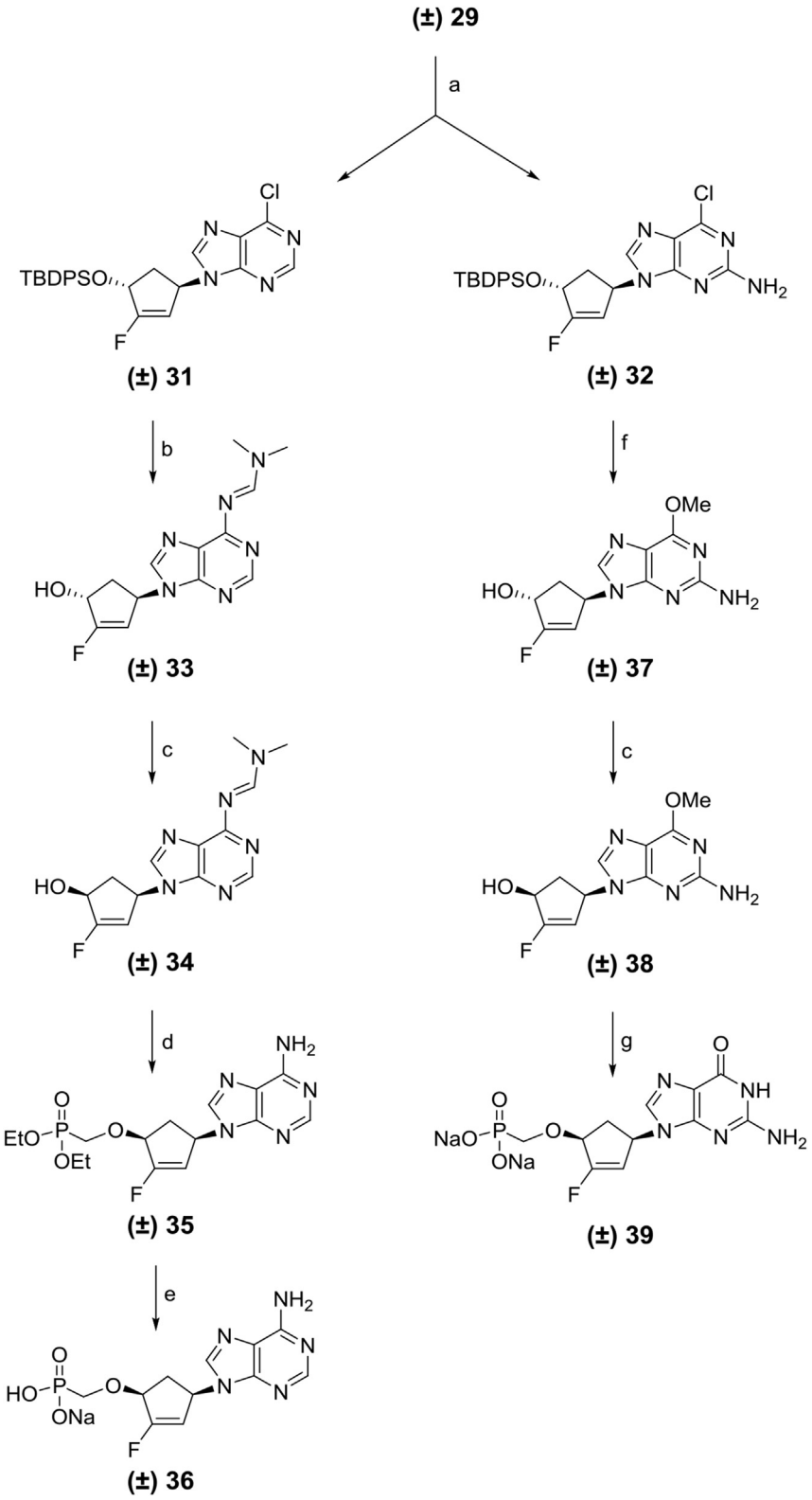
All air and/or moisture sensitive reactions were carried out under an argon atmosphere with dry or freshly distilled solvents and using standard syringe-cannula/septa techniques. All corresponding glassware was oven-dried (100 °C) and/or carefully dried in line with a flameless heat gun. All solvents were distilled under argon atmosphere: THF from a blue solution of sodium-benzophenone ketyl radical prior to use, CH_2Cl_2 and DMF from CaH_2, pyridine from KOH. Routine monitoring of reactions was performed using Merck silica gel 60 F_{254} aluminium supported TLC plates; spots were visualized using a UV light and ethanolic acidic *p*-anisaldehyde solution or 5% ethanolic sulfuric acid solution, followed by heating. Purification by column chromatography was performed with silica gel 60 (230–400 mesh) or with reversed phase silica gel (RP-18, 25–40 μm). Ion exchange chromatography was performed on DOWEX 50WX8-200 resins (Na^+ form). ^1H, ^{13}C NMR, ^{31}P and ^{19}F spectra were recorded in $CDCl_3$, MeOD, D_2O or DMSO-d6 solutions on Brucker AM-600, DRX 400, AM-300, DPX 200 spectrometers. Chemicals shifts (δ) are reported in parts per millions using residual non deuterated solvents as internal references and signals are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). MS and HRMS were recorded in the positive or negative mode on a Micromass Q-TOF Waters. UV spectra were recorded with an Uvikon 931 (Kontron) spectrophotometer, λ are expressed in nm and ε in $L.mol^{-1}.cm^{-1}$.

4.1.1. (±)-4-Hydroxy-2-cyclopentenone

A solution of furfuryl alcohol (50.11 g, 0.51 mol) in H_2O (1.5 L) was treated with KH_2PO_4 (2.50 g, 18 mmol). The solution was adjusted to pH = 4.1 with H_3PO_4, then heated to 90 °C for 36 h. The cooled solution was extracted with AcOEt. The combined organic layers were washed with H_2O and the aqueous layers combined and evaporated to give a red oil. The red oil was dissolved in AcOEt, dried ($MgSO_4$) filtered through a pad of Celite and the filtrate was evaporated *in vacuo* to give (±)-4-Hydroxy-2-cyclopentenone as a dark oil (25 g, 0,26 mol, 50%) which was used without further purification. The physicochemical properties were similar to those previously reported [5].

4.1.2. (±)-4-tert-butyldimethylsilyloxy-2-cyclopentenone (*1*)

To a solution of (±)-4-Hydroxy-2-cyclopentenone (45.11 g, 460 mmol) and Et_3N (102 mL) in THF (230 mL) was added with DMAP (1.12 g, 9.2 mmol). The solution was cooled to 0 °C and treated with portionwise addition of TBDMSCl (65.78 g, 437 mmol) to keep the temperature of the reaction mixture below 10 °C. The resulting mixture was stirred at rt for three days, then poured into aqueous 0.5 N HCl. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic phases were combined, washed with aqueous 0.5 N HCl, saturated $NaHCO_3$, brine, dried ($MgSO_4$), filtered, and the filtrate was evaporated to give an oil. This last was purified by distillation (P = 0,05 mbar, T = 73–74 °C) to give (±) **1** as a colorless oil (60.65 g, 286 mmol, 62%). The physicochemical properties were similar to those previously reported [5].



Scheme 5. Synthesis of the 3′-fluoro-5′-norcarbocyclic nucleoside phosphonate (±) **36** and (±) **39**. Reagents and conditions: (a) 2-amino-6-chloropurine or 6-chloropurine, PPh_3, DIAD, THF, rt, 4 h, 54% for (±) **31**; 52% for (±) **32**; (b) i) NH_3/MeOH, 70 °C, 30 h; ii) DMF-dimethylacetal, DMF, 50 °C, 15 h, 70% over two steps; (c) i) benzoic acid, PPh_3, DIAD, THF, rt, 3 h; ii) K_2CO_3, MeOH, rt; 2 h, 85% over two steps for (±) **34**; 16 h, 93% over two steps (±) **38**; (d) $(Et_2O)POCH_2OTs$, LiO*t*Bu, THF, 60 °C, 3 days, 71%; (e) TMSBr, DMF, rt, 38 h, 42% overall yield; (f) K_2CO_3, MeOH, reflux, 4 h, 80%; (g) i) $(Et_2O)POCH_2OTs$, LiO*t*Bu, THF, 60 °C, 3 days; ii) TMSBr, DMF, rt, 16 h, 23% over two steps.

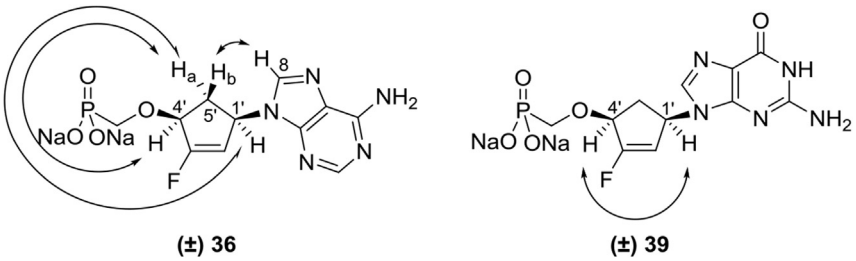


Fig. 3. Selected NOE effects on compounds (±) **36** and (±) **39**.

Table 1
Anti HIV-1 LAI and cytotoxic properties of 3′-halo-5′-norcarbocyclic nucleoside phosphonates and reference compound (*R*)-PMPA in human peripheral blood mononuclear cells (PBMC).

Compounds	EC_{50} (μM)[a]	CC_{50} (μM)[b]
(±) **12**	5.9	≥10
(±) **(15)**	≥10	≥10
(±) **18**	≥10	≥10
(±) **20**	≥10	≥10
(±) **(36)**	0.88	≥10
(±) **39**	≥10	≥10
(*R*)-PMPA	1.1	≥10

[a] EC_{50} Effective concentration of drug required to reduce viral replication by 50%. Data are the mean from 3 blood donors.
[b] CC_{50} Cytotoxic concentration of drug required to reduce cell growth by 50%. Data are the mean from 3 blood donors.

*4.1.3. (±)-4-tert-butyldimethylsilyloxy-2-iodocyclopent-2-enone (**2**)*

To a stirred solution of (±) **1** (9.92 g, 46.7 mmol) in CH_2Cl_2 (390 mL) under an argon atmosphere were added sublimated I_2 (17.78 g, 70.0 mmol) and pyridinium dichromate (5.27 g, 14.0 mmol). The reaction mixture was stirred at rt for two days. Water was added to the reaction mixture and the emulsion was filtrated through a pad of Celite. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with $Na_2S_2O_3$, brine, dried ($MgSO_4$), filtrated and the filtrate was evaporated to give an oil which was purified by column chromatography on silica gel (Petroleum Ether/Et_2O 95/5) to give (±) **2** (13.59 g, 40.1 mmol, 86%) as a brown oil. The physicochemical properties were similar to those previously reported [7].

*4.1.4. (±)-4-tert-butyldimethylsilyloxy-2-iodocyclopent-2-enol (**3**) and (**4**)*

To a stirred solution of (±) **2** (23.15 g, 68.4 mmol) in CH_3OH (360 mL) was added $CeCl_3 \cdot 7H_2O$ (25.50 g, 68.4 mmol). The reaction mixture was stirred at rt for 1 h and then cooled to −78 °C $NaBH_4$ (3.11 g, 82.2 mmol) was added portionwise and the reaction mixture was stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 and saturated NH_4Cl and water were added. The phases were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and volatiles were evaporated. Purification by column chromatography on silica gel (CH_2Cl_2) gave (±) **3** (19.75 g, 58.0 mmol, 85%), and its diastereoisomer (±) **4** (1.80 g, 5.3 mmol, 8%) as a white solid. The physicochemical properties of (±) **3** and (±) **4** were similar to those previously reported [10].

*4.1.5. (±)-4-{[tert-butyl(dimethyl)silyl]oxy}-2-iodo-cyclopent-2-en-1-yl benzoate (**5**)*

From compound (±) **3**: To a stirred solution of PPh_3 (10.25 g, 39.1 mmol) and BzOH (4.77 g, 39.1 mmol) in dry THF (90 mL) at rt was cannulated a solution of (±) **3** (11.08 g, 32.5 mmol) in dry THF (160 mL). The reaction mixture was cooled to 0 °C and DIAD (7.68 mL, 39.1 mmol) was added dropwise. The solution was stirred for 1 h and concentrated under reduced pressure. Purification by column chromatography with petroleum ether/AcOEt (98/2) gave (±) **5** (14.29 g, 32.9 mmol, 98%) as a yellow oil. Rf = 0.27 (2% AcOEt in petroleum ether).

From compound (±) **4**: Compound (±) **4** (1.75 g, 5.1 mmol) was dissolved at 0 °C in dry pyridine/CH_2Cl_2 (96/4, 30 mL) and BzCl (0.89 mL, 7.7 mmol) was added under an argon atmosphere. The reaction mixture was stirred at rt for 12 h then poured at 0 °C into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with $NaHCO_3$, water and brine then dried, filtered, and concentrated *in vacuo*. Purification by column chromatography with a stepwise gradient of diethyl ether (1–2%) in petroleum ether gave (±) **5** (1.72 g, 75%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (d, *J* = 9.2 Hz, 2H, ArH), 7.60–7.55 (m, 1H, ArH), 7.48–7.43 (m, 2H, ArH), 6.48 (d, *J* = 1.3 Hz, 1H, H3), 6.02–5.98 (m, 1H, H1), 4.96–4.91 (m, 1H, H4), 2.23–2.29 (m, 2H, H5), 0.90 (s, 9H, *t*-Bu), 0.09 (s, 6H, 2 × CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.2 (Cq), 148.9 (C3), 133.3 (CAr), 130.1 (Cq), 129.9 (2 × CAr), 128.5 (2 × CAr), 98.0 (C2), 83.8 (C1), 76.6 (C4), 41.7 (C5), 25.9 (3 × CH_3), 18.2 (Cq), −4.62 (CH_3), −4.66 (CH_3). HRMS (ASAP$^+$): calcd. for $C_{18}H_{24}IOSi$ $[M-H]^+$ 443.0539; found 443.0541.

*4.1.6. (±)-4-Hydroxy-2-iodo-2-cyclopenten-1-yl benzoate (**6**)*

To a stirred solution of (±) **5** (37.94 g, 85.4 mmol) in dry THF (600 mL) at 0 °C was added dropwise a 1 M solution of TBAF (102 mL, 102.0 mmol). The reaction mixture was stirred at 0 °C for 2 h and then concentrated *in vacuo*. The residual oil was purified by column chromatography with a stepwise gradient of AcOEt (25–50%) in petroleum ether to afford (±) **6** (26.98 g, 81.7 mmol, 95%) as a white solid. Rf = 0.27 (30% AcOEt in petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07–8.05 (m, 2H, ArH), 7.61–7.56 (m, 1H, ArH), 7.48–7.43 (m, 1H, ArH), 6.58 (m, 1H, H3), 6.09–6.04 (m, 1H, H1), 4.98–4.93 (m, 1H, H4), 2.40–2.36 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.2 (Cq), 147.8 (C3), 133.4 (CAr), 129.9 (2 × CAr), 128.5 (2 × CAr), 100.1 (C2), 83.3 (C1), 76.4 (C4), 41.4 (C5).

*4.1.7. (±)-4-(6-Chloro-9H-purin-9-yl)-2-iodo-2-cyclopenten-1-yl benzoate (**7**)*

To a stirred solution of PPh_3 (4.31 g, 16.4 mmol) and 6-chloropurine (2.54 g, 16.4 mmol) in dry THF (120 mL) at 0 °C under an argon atmosphere, was added dropwise DIAD (3.23 mL, 16.4 mmol) over 15 min. After stirring for 1 h, a solution of (±) **6** (2.50 g, 7.5 mmol) in dry THF (60 mL) was added. The reaction mixture was stirred at rt for 2 h then concentrated *in vacuo*. The resulting syrup was purified by silica gel chromatography with a stepwise gradient of AcOEt (10–50%) in petroleum ether to give (±) **7** (3.05 g, 6.5 mmol, 43%) as a white foam. Rf = 0.27 (40% AcOEt in petroleum ether). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.76 (s, 1H, H2), 8.25 (s, 1H, H8), 8.08–8.04 (m, 2H, ArH), 7.64–7.59 (m, 1H, ArH), 7.51–7.45 (m, 2H, ArH), 6.63 (d, *J* = 2.4 Hz, 1H, H3′), 6.02 (dd, *J* = 7.5, 3.3 Hz, 1H, H1′), 5.76 (dt, *J* = 7.9, 3.0 Hz, 1H, H4′), 3.37 (ddd, *J* = 15.1, 8.3, 7.5 Hz, 1H, H5′a), 2.20 (dt, *J* = 15.1, 3.5 Hz, 1H, H5′b). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.6 (Cq), 152.3 (C2), 151.3 (Cq), 143.1 (C8), 141.1 (C3′), 133.8 (2 × CAr), 131.7 (Cq), 129.9 (Cq), 129.2 (Cq), 128.8 (2 × CAr), 102.4 (C2′), 81.6 (C1′), 58.7 (C4′), 39.4 (C5′). MS (ESI$^+$): *m/z* = 467 (M + H)$^+$. UV (EtOH 95) λ_{max} = 265 nm (ε_{max} = 11000). HRMS (ESI$^+$): calcd. for $C_{17}H_{13}ClIN_4O_2$ [M+H]$^+$ 466.9772; found 466.9769.

*4.1.8. (±)-4-(6-Amino-9H-purin-9-yl)-2-iodo-2-cyclopenten-1-ol (**9**)*

A solution of (±) **7** (1.23 g, 2.6 mmol) in methanolic ammonia (2 M, 100 mL) was heated at 70 °C in a Parr high pressure reactor for 20 h. The mixture was filtered, the solid was washed with CH_3OH and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography with a stepwise gradient of CH_3OH (0–8%) in CH_2Cl_2 to give (±) **9** (0.75 g, 81%) as a yellow solid. Rf = 0.11 (5% CH_3OH in CH_2Cl_2). ^{1}H NMR (DMSO-d6, 300 MHz): δ 8.13 (s, 1H, H2), 8.09 (s, 1H, H8), 7.30 (s, 2H, NH_2), 6.43 (dd, *J* = 2.3, 0.8 Hz, 1H, H3′), 6.09 (d, *J* = 8.3 Hz, 1H, OH), 5.41–5.36 (m, 1H, H4′), 4.57–4.51 (m, 1H, H1′), 2.97 (ddd, *J* = 13.8, 8.2, 7.6 Hz, 1H, H5′a), 1.92 (dt, *J* = 13.8, 4.5 Hz, 1H, H5′b). ^{13}C NMR (DMSO-d6, 75 MHz): δ 156.1 (Cq), 152.2 (C2), 148.7 (Cq), 139.2 (C3′), 138.4 (C8), 119.0 (Cq), 109.9 (C2′), 79.0 (C1′), 58.2 (C4′), 40.2 (C5′). MS (ESI$^+$): *m/z* = 344 (M + H)$^+$. UV (EtOH 95) λ_{max} = 261 nm (ε_{max} = 20500). HRMS (ESI$^+$): calcd. for $C_{10}H_{11}IN_5O$ [M+H]$^+$ 344.0008; found 344.0003.

*4.1.9. (±)-N′-{9-[-4-Hydroxy-3-iodo-2-cyclopenten-1-yl]-9H-purin-6-yl}-N,N-dimethylimidoformamide (**10**)*

To a stirred solution of (±) **9** (0.70 g, 4.1 mmol) in dry DMF (10 mL) under argon atmosphere was added DMF-dimethylacetal (0.82 mL, 6.1 mmol) at rt. The mixture was heated at 50 °C for 4 h then concentrated *in vacuo*. The residue was purified by silica gel chromatography with CH_2Cl_2/CH_3OH (95/5) to afford (±) **10** (0.76 g, 93%) as a white foam. Rf = 0.58 (10% CH_3OH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.93 (s, 1H, H2), 8.44 (s, 1H, H8), 7.88 (s, 1H, N=CH-N), 7.10 (br s, 1H, OH), 6.15 (d, *J* = 2.5 Hz, 1H, H2′), 5.20 (ddd, *J* = 9.3, 2.6, 1.6 Hz, 1H, H1′), 4.68 (d, *J* = 6.8 Hz, 1H, H4′), 3.24 (d, *J* = 0.8 Hz, 3H, CH_3), 3.20 (d, *J* = 0.8 Hz, 3H, CH_3), 3.11–3.01 (m, 1H, H5′a), 2.41 (d, *J* = 15.3 Hz, 1H, H5′b). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.0 (Cq), 158.3 (N=CH-N), 151.6 (C2), 150.1 (Cq), 141.6 (C3′), 137.3 (C8), 127.4 (Cq), 110.1 (C2′), 81.5 (C4′), 60.7 (C1′), 41.5 (CH_3), 38.7 (C5′), 35.3 (CH_3). MS (ESI$^+$): *m/z* = 399 (M + H)$^+$. UV (EtOH 95) λ_{max} = 312 nm (ε_{max} = 28000). HRMS (ESI$^+$): calcd. for $C_{13}H_{16}IN_6O$ [M+H]$^+$ 399.0430; found 399.0433.

*4.1.10. (±)-diethyl {[-4-(6-amino-9H-purin-9-yl)-2-iodo-2-cyclopenten-1-yl]oxy}methylphosphonate (**11**)*

To a stirred solution of (±) **10** (0.72 g, 1.8 mmol) in dry THF (25 mL) at 0 °C was added dropwise LiO*t*Bu (2.2 M solution in THF, 3.27 mL, 7.2 mmol) under an argon atmosphere. After stirring for 1 h at 0 °C diethyl *p*-toluene sulfonyloxymethyl phosphonate (3.08 g, 9.6 mmol) was added and the mixture was stirred for 2 days at rt. Few drops of AcOH were added and the mixture was concentrated *in vacuo*. The crude product was solubilized in an AcOH/H_2O/CH_3OH (9/1/1) solution (9 mL) and stirred for two days at rt before concentration *in vacuo*. Purification by silica gel chromatography with AcOEt/CH_3OH (80/20) gave (±) **11** (0.647 g, 73%) as a white foam. Rf = 0.25 (20% CH_3OH in AcOEt. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 7.93 (s, 1H), 6.44 (d, *J* = 2.5 Hz, 1H, H3′), 6.21 (br s, 2H, NH_2), 5.54 (dt, *J* = 8.3, 3.1 Hz, 1H, H4′), 4.59 (dd, *J* = 6.9, 3.0 Hz, 1H, H1′), 4.03 and 3.93 (ABX, *J* = 13.7, 8.9 Hz, 2H, CH_2), 2.99 (ddd, *J* = 15.0, 8.2, 7.3 Hz, 1H, H5′a), 2.13 (dt, *J* = 14.6, 3.3 H, 1H, H5′b), 1.34 (t, *J* = 7.1 Hz, 3H, CH_3), 1.32 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8 (Cq), 153.1 (C2), 149.5 (Cq), 141.2 (C3′), 138.9 (C8), 119.5 (Cq), 102.6 (C2′), 89.3 (d, *J* = 11.8, C1′), 64.3 (d, *J* = 166.8 Hz, OCH_2P), 62.8–62.7 (m, 2 × CH_2), 57.4 (C4′), 38.2 (C5′), 16.6 (d, *J* = 6.0 Hz, 2 × CH_3). ^{31}P (D_2O, 162 MHz): δ 20.1. MS (ESI$^+$): *m/z* = 494 (M + H)$^+$. UV (EtOH 95) λ_{max} = 261 nm (ε_{max} = 16400). HRMS (ESI$^+$): calcd. for $C_{15}H_{22}IN_5O_4P$ [M+H]$^+$ 494.0454; found 494.0458.

*4.1.11. (±)-{[-4-(6-Amino-9H-purin-9-yl)-2-iodo-2-cyclopenten-1-yl]oxy}methylphosphonic acid (**12**)*

To a stirred solution of phosphonate ester (±) **11** (247 mg, 1.0 mmol) in dry DMF (8 mL) at 0 °C under argon atmosphere was added dropwise TMSBr (1.97 mL, 15.1 mmol). The solution was stirred at rt for 12 h then neutralized with an aqueous triethylammonium hydrogen bicarbonate solution (1 M, pH 7) and concentrated to dryness under reduce pressure. Reverse-phase column chromatography of the residue with H_2O/CH_3OH (100/0 to 87/13) gave (±) **12** (147 mg, 67%) as a white solid. Rf = 0.22 (isopropanol/NH_4OH/H_2O: 7/2/1). ^{1}H NMR (D_2O, 400 MHz): δ 8.20 (s, 1H, H2), 8.20 (s, 1H, H8), 6.60 (dd, *J* = 2.3, 1.0 Hz, 1H, H3′), 5.46–5.42 (m, 1H, H4′), 4.76–4.73 (m, 1H, H1′), 3.64 (d, *J* = 9.1 Hz, 2H, P-CH_2-O), 3.14 (ddd, *J* = 14.3, 8.3, 7.5 Hz, 1H, H5′a), 2.16 (dt, *J* = 14.3, 4.7 Hz, 1H, H5′b). ^{13}C NMR (D_2O, 100 MHz): δ 155.4 (Cq), 152.3 (C2), 148.4 (Cq), 140.6 (C8), 140.0 (C3′), 118.5 (Cq), 104.0 (C2′), 88.1 (d, *J* = 11.4 Hz, C1′), 67.5 (d, *J* = 149.9 Hz, P-CH_2-O), 58.3 (C4′), 37.2 (C5′). ^{31}P NMR (D_2O, 162 MHz): δ 12.9. MS (ESI$^+$): *m/z* = 438 (M + H)$^+$. UV (EtOH 95) λ_{max} = 261 nm (ε_{max} = 8100). HRMS (ESI$^+$): calcd. for $C_{11}H_{14}IN_5O_4P$ [M+H]$^+$ 437.9828; found 437.9823.

*4.1.12. (±)-4-[6-(cyclopropylamino)-9H-purin-9-yl]-2-iodo-2-cyclopenten-1-ol (**13**)*

To a solution of (±) **7** (786 mg, 1.7 mmol) in dry THF (20 mL) under argon atmosphere was added at rt cyclopropylamine (3.5 mL, 50.5 mmol). The mixture was stirred at 50 °C for 4 h and concentrated *in vacuo*. Purification by silica gel chromatography (AcOEt) gave the benzoate derivative (773 mg, 1.6 mmol, 94%) as a white foam. This intermediate (707 mg, 1.5 mmol) was dissolved in dry CH_3OH (21 mL) and anhydrous K_2CO_3 (501 mg, 3.6 mmol) was added at rt. After stirring for 2 h, the mixture was filtered through a sintered funnel covered with Celite and silica gel and concentrated *in vacuo*. Purification by silica gel chromatography with a stepwise gradient of CH_3OH (1–6%) in CH_2Cl_2 gave (±) **13** (474 mg, 1.2 mmol, 85%) as a white foam. Rf = 0.23 (3% CH_3OH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H, H2), 7.75 (s, 1H, H8), 6.17 (s, 1H, NH), 6.14 (d, *J* = 2.6 Hz, 1H, H3′), 5.16 (ddd, *J* = 9.3, 2.3, 1.4 Hz, 1H, H4′), 4.68 (d, *J* = 7.5 Hz, 1H, H1′), 3.10–3.02 (m, 2H, CH + H5′a), 2.41 (d, *J* = 15.4 Hz, 1H, H5′b), 0.95–0.90 (m, 2H, CH_2), 0.66–0.62 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.2 (Cq), 152.4 (C2), 139.8 (C8), 137.3 (C3′), 121.3 (Cq), 110.3 (C2′), 81.5 (C1′), 60.8 (C4′), 38.6 (C5′), 23.8 (CH), 7.5 (2 × CH_2). MS (ESI$^+$): *m/z* = 484 (M + H)$^+$. UV (EtOH 95) λ_{max} = 272 nm (ε_{max} = 19000). HRMS (ESI$^+$): calcd. for $C_{13}H_{15}IN_5O$ [M+H]$^+$ 384.0321; found 384.0319.

*4.1.13. (±)-diethyl ({-4-[6-(cyclopropylamino)-9H-purin-9-yl]-2-iodo-2-cyclopenten-1-yl}oxy)methylphosphonate (**14**)*

To a stirred solution of (±) **13** (248 mg, 0.65 mmol) in dry THF (10 mL) at 0 °C under an argon atmosphere was added LiO*t*Bu (2.2 M solution in THF, 1.18 mL, 2.59 mmol). The solution was stirred at 0 °C for 1 h until addition of diethyl *p*-toluene sulfonyloxymethyl phosphonate (1.11 g, 3.45 mmol). The reaction mixture was stirred at rt for 4 days, and then quenched by addition of AcOH (few drops). Concentration to dryness followed by purification by silica gel chromatography with a stepwise gradient of CH_3OH (1–10%) in CH_2Cl_2 gave compound (±) **14** (yellow oil, 262 mg, 76%). Rf = 0.20 (5% CH_3OH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.38 (s, 1H, H2), 7.82 (s, 1H, H8), 6.41 (br s, 1H, NH), 6.39 (d, J = 2.2 Hz, 1H, H3′), 5.48 (dt, J = 7.7, 2.8 Hz, 1H, H4′), 4.54 (dd, J = 6.9, 3.0 Hz, 1H, H1′), 4.18–4.06 (m, 4H, 2 × CH_2), 3.97 and 3.87 (ABX, J = 13.8, 8.8 Hz, 2H, CH_2), 3.03–2.90 (m, 2H, CH + H5′a), 2.06 (dt, J = 14.6, 3.4 Hz, 1H, H5′b), 1.27 (q, J = 7.2 Hz, 6H, 2 × CH_3), 0.88–0.81 (m, 2H, CH_2), 0.60–0.55 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.8 (Cq), 153.1 (C2), 148.5 (Cq), 141.0 (C3′), 138.1 (C8), 119.6 (Cq), 102.5 (C2′), 89.1 (d, J = 11.2 Hz, C1′), 64.1 (d, J = 166.5 Hz, OCH_2P), 62.6 (d, J = 6.5 Hz, 2 × CH_2), 57.3 (C4′), 38.1 (C5′), 23.7 (CH), 16.5–16.4 (m, 2 × CH_3), 7.3 (2 × CH_2). ^{31}P ($CDCl_3$, 121 MHz): 20.08 ppm MS (ESI^+): m/z = 534 (M + H)$^+$. UV (EtOH 95) λ_{max} = 271 nm (ε_{max} = 18700). HRMS (ESI^+): calcd. for $C_{18}H_{26}IN_5O_4P$ $[M+H]^+$ 534.0767; found 534.0764.

*4.1.14. (±)-disodium ({-4-[6-(cyclopropylamino)-9H-purin-9-yl]-2-iodo-2-cyclopenten-1-yl}oxy)methyl phosphonate (**15**)*

Compound (±) **15** (white solid, 115 mg, 0.2 mmol, 69%) was synthesized from (±) **14** (171 mg, 0.3 mmol) using the similar procedure as described for (±) **12** followed by ion exchange on DOWEX 50WX2 (Na^+ form) and freeze-drying. Rf = 0.42 (isopropanol/NH_4OH/H_2O: 7/2/1). ^{1}H NMR (D_2O, 400 MHz): δ 8.17 (s, 1H, H2), 8.08 (s, 1H, H8), 6.56 (br s, 1H, H3′), 5.37 (br s, 1H, H4′), 4.73 (br s, 1H, H1′), 3.72 (d, J = 9.1 Hz, P-CH_2-O), 3.14–3.07 (m, 1H, H5′a), 2.80 (br s, 1H, CH), 2.10 (br d, J = 14.3 Hz, 1H, H5′b), 0.90 (d, J = 6.4 Hz, 2H, CH_2), 0.65 (s, 2H, CH_2). ^{13}C NMR (D_2O, 100 MHz): δ 155.5 (Cq), 152.3 (C2), 147.5 (Cq), 140.3 (C3′), 140.0 (C8), 118.9 (Cq), 103.9 (C2′), 88.6 (d, J = 11.6 Hz, C1′), 66.5 (d, J = 153.9 Hz, O-CH_2-P), 58.5 (C4′), 37.4 (C5′), 23.4 (CH), 6.7 (2 × CH_2). ^{31}P NMR (D_2O, 162 MHz): δ 14.3 ppm. MS (ESI^+): m/z = 478 (M + H)$^+$. UV (EtOH 95) λ_{max} = 271 nm (ε_{max} = 17600). HRMS (ESI^+): calcd. for $C_{14}H_{18}IN_5O_4P$ $[M+H]^+$ 478.0141; found 478.0149.

*4.1.15. (±)-2-iodo-4-(6-methoxy-9H-purin-9-yl)-2-cyclopenten-1-ol (**16**)*

To a stirred solution of (±) **7** (182 mg, 0.4 mmol) in CH_3OH (5.6 mL) at rt under an argon atmosphere was added anhydrous K_2CO_3 (135 mg, 1.0 mmol) by portionwise. After stirring overnight, the mixture was filtered through a sintered funnel covered with Celite and concentrated. Purification by silica gel chromatography with a stepwise gradient of AcOEt (70–75%) in petroleum ether gave (±) **16** (107 mg, 0.3 mmol, 75%) as a white foam. Rf = 0.30 (AcOEt). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.47 (s, 1H, H2), 7.95 (s, H8), 6.49 (d, J = 10.7 Hz, 1H, OH), 6.17 (d, J = 2.6 Hz, 1H, H3′), 5.26 (dt, J = 9.3, 2.2 Hz, 1H, H4′), 4.71–4.67 (m, 1H, H1′), 4.16 (s, 3H, OCH_3), 3.09 (ddd, J = 15.5, 9.2, 7.9 Hz, 1H, H5′a), 2.38 (d, J = 15.3 Hz, 1H, H5′b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5 (Cq), 151.5 (C2), 150.5 (Cq), 142.0 (C8), 137.3 (C3′), 123.0 (Cq), 110.2 (C2′), 81.3 (C1′), 60.7 (C4′), 54.5 (OCH_3), 38.8 (C5′). MS (ESI^+): m/z = 359 (M + H)$^+$. UV (EtOH 95) λ_{max} = 249 nm (ε_{max} = 10600). HRMS (ESI^+): calcd. for $C_{11}H_{12}IN_4O_2$ $[M+H]^+$ 359.0005; found 359.0002.

*4.1.16. (±)-diethyl {[-2-iodo-4-(6-methoxy-9H-purin-9-yl)-2-cyclopenten-1-yl]oxy}methylphosphonate (**17**)*

Compound (±) **17** (440 mg, 0.9 mmol, 67%) was synthesized from (±) **16** (463 mg, 1.3 mmol) using a similar procedure as described for (±) **14** with 3 eq. of LiO*t*Bu, 4 eq. of diethyl *p*-toluene sulfonyloxymethyl phosphonate and stirred for 8 days at rt. Rf = 0.22 (5% CH_3OH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (s, 1H, H2), 7.98 (s, 1H, H8), 6.41 (d, J = 2.4 Hz, 1H, H3′), 5.53 (dt, J = 8.2, 3.0 Hz, 1H, H4′), 4.56 (dd, J = 7.0, 3.1 Hz, 1H, H1′), 4.18–4.06 (m, 4H, 2 × CH_2), 4.12 (s, 3H, OCH_3), 4.00 and 3.89 (ABX, J = 13.8, 8.7 Hz, 2H, CH_2), 2.98 (m, ddd, J = 15.2, 8.2, 7.3 Hz, 1H, H5′a), 2.11 (dt, J = 14.6, 3.3 Hz, 1H, H5′b), 1.31–1.24 (m, 6H, 2 × CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.0 (Cq), 152.0 (C2), 151.4 (Cq), 140.7 (C8), 140.5 (C3′), 121.4 (Cq), 102.8 (C2′), 89.2 (d, J = 10.9 Hz, C4′), 64.2 (d, J = 166.3 Hz, OCH_2P), 62.8 (d, J = 6.8 Hz, CH_2), 62.7 (d, J = 6.8 Hz, CH_2), 57.7 (C1′), 54.2 (OCH_3), 38.1 (C5′), 16.5–16.4 (m, 2xCH_3). ^{31}P NMR (D_2O, 162 MHz): δ 19.9 ppm. MS (ESI^+): m/z = 509 (M + H)$^+$. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 12700). HRMS (ESI^+): calcd. for $C_{16}H_{23}IN_4O_5P$ $[M+H]^+$ 509.0451; found 509.0445.

*4.1.17. (±)-disodium {[-2-iodo-4-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2-cyclopenten-1-yl]oxy}methylphosphonate (**18**)*

Compound (±) **18** (white solid, 107 mg, 0.2 mmol, 72%) was synthesized from (±) **17** (156 mg, 0.3 mmol) using the similar procedure as described for (±) **15**. Rf = 0.27 (isopropanol/NH_4OH/H_2O: 5/1/1). ^{1}H NMR (D_2O, 400 MHz): δ 8.14–8.13 (m, 2H, H2, H8), 6.56 (s, 1H, H3′), 5.42 (br s, 1H, H4′), 4.70 (br s, 1H, H1′), 3.78–3.68 (m, 2H, P-CH_2-O), 3.13–3.06 (m, 1H, H5′a), 2.15 (d, J = 14.3 Hz, 1H, H5′b). ^{13}C NMR (D_2O, 100 MHz): δ 158.4 (Cq), 148.2 (Cq), 145.7 (C2), 140.3 (C3′), 140.1 (C8), 123.3 (Cq), 103.7 (C2′), 88.4 (d, J = 12.0 Hz, C1′), 66.2 (d, J = 154.3 Hz, P-CH_2-O), 58.8 (C4′), 37.1 (C5′). ^{31}P NMR (D_2O, 162 MHz): δ 14.5 ppm. MS (ESI^+): m/z = 439 (M + H)$^+$. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 8500). HRMS (ESI^+): calcd. for $C_{11}H_{13}IN_4O_5P$ $[M+H]^+$ 438.9668; found 438.9673.

*4.1.18. (±)-4-(2-Amino-6-methoxy-9H-purin-9-yl)-2-iodo-2-cyclopenten-1-ol (**8**)*

To a stirred solution of 2-amino-6-chloro-9*H*-purine (1.25 g, 7.4 mmol) and PPh_3 (1.95 g, 7.4 mmol) in dry THF (240 mL), at 0 °C under an argon atmosphere was added dropwise DIAD (1.44 mL, 7.4 mmol) over 5 min. After stirring for 1 h a solution of (±) **6** (1.01 g, 3.1 mmol) in dry THF (80 mL) was added, and stirred at rt overnight. The solution was concentrated *in vacuo* and the resulting syrup was filtered through a Celite pad. Partial purification by silica gel chromatography with a stepwise gradient of AcOEt (25–50%) in petroleum ether gave benzoate intermediate as a white solid. This intermediate was dissolved in dry CH_3OH (30 mL) and anhydrous K_2CO_3 (4.10 g, 29.6 mmol) was added at rt. After stirring overnight, the mixture was filtered through a sintered funnel covered with Celite and silica gel and concentrated *in vacuo*. Purification by silica gel chromatography (AcOEt) gave (±) **8** (504 mg, 1.3 mmol, 44%) as a white foam. Rf = 0.15 (AcOEt). ^{1}H NMR (MeOD, 400 MHz): δ 7.83 (s, 1H, H8), 6.36 (d, J = 2.2 Hz, 1H, H3′), 5.35–5.31 (m, 1H, H4′), 4.64 (dd, J = 7.4, 3.5 Hz, 1H, H1′), 4.04 (s, 3H, OCH_3), 3.05 (dt, J = 14.4, 8.1 Hz, 1H, H5′a), 2.04 (dt, J = 14.4, 3.9 Hz, 1H, H5′b). ^{13}C NMR (MeOD, 100 MHz): δ 162.7 (Cq), 161.5 (Cq), 154.1 (Cq), 140.0 (C2′), 139.7 (C8), 115.6 (Cq), 109.5 (Cq), 81.4 (C4′), 59.9 (C1′), 54.2 (OCH_3), 40.9 (C5′). MS (ESI^+): m/z = 374 (M + H)$^+$. UV (EtOH 95) λ_{max} = 252 nm (ε_{max} = 8400), λ_{max} = 280 nm (ε_{max} = 10000). HRMS (ESI^+): calcd. for $C_{11}H_{13}IN_5O_2$ $[M+H]^+$ 374.0114; found 374.0117.

*4.1.19. (±)-diethyl {[-4-(2-amino-6-methoxy-9H-purin-9-yl)-2-iodo-2-cyclopenten-1-yl]oxy}methylphosphonate (**19**)*

Compound (±) **19** (yellow oil, 342 mg, 0.6 mmol, 53%) was synthesized from (±) **8** (460 mg, 1.2 mmol) using the similar

procedure as described for (±) **14** with 3 eq. of LiOtBu, 4.5 eq. of diethyl *p*-toluene sulfonyloxymethyl phosphonate and stirred for 2 days at rt. Purification was achieved with AcOEt/CH_3OH (95/5). Rf = 0.47 (5% CH_3OH in EtOAc). 1H NMR ($CDCl_3$, 400 MHz): δ 7.65 (s, 1H, H8), 6.39 (d, *J* = 1.8 Hz, 1H, H3′), 5.31–5.30 (m, 1H, H1′), 5.01 (s, 2H, NH_2), 4.65 (dd, *J* = 7.1, 3.8 Hz, 1H, H4′), 4.23 (dd, *J* = 13.9, 9.6 Hz, 1H, OCH_2P), 4.20–4.16 (m, 4H, 2 × CH_2), 4.05 (s, 3H, OCH_3), 3.96 (dd, *J* = 14.0, 8.3 Hz, 1H, OCH_2P), 2.95–2.90 (m, 1H, H5′a), 2.28 (dt, *J* = 14.5, 4.1 Hz, 1H, H5′b), 1.34 (t, *J* = 7.0 Hz, 6H, 2 × CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.7 (Cq), 159.4 (Cq), 153.4 (Cq), 141.7 (C3′), 137.8 (C8), 115.8 (Cq), 102.2 (Cq), 88.8 (d, *J* = 11.2 Hz, C1′), 62.9 (d, *J* = 166.0 Hz, OCH_2P), 62.8 (d, *J* = 8.6 Hz, CH_2), 62.7 (d, *J* = 8.8 Hz, CH_2), 57.9 (C4′), 53.9 (OCH_3), 36.8 (C5′), 16.6–16.5 (m, 2 × CH_3). ^{31}P NMR ($CDCl_3$, 162 MHz): δ 20.8. MS (ESI^+): *m/z* = 524 $(M + H)^+$. UV (EtOH 95) λ_{max} = 246 nm (ε_{max} = 6700), λ_{max} = 282 nm (ε_{max} = 6600). HRMS (ESI^+): calcd. for $C_{16}H_{24}IN_5O_5P$ $[M+H]^+$ 524.0560; found 524.0524.

4.1.20. (±)-{[-4-(2-Amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-iodo-2-cyclopenten-1-yl]oxy}methylphosphonic acid (**20**)

Compound (±) **20** (white solid, 66 mg, 0.15 mmol, 58%) was synthesized from (±) **19** (130 mg, 0.25 mmol) using the similar procedure as described for (±) **15**. Rf = 0.13 (*i*PrOH/NH_4OH/H_2O: 7/2/1). ^1H NMR (D_2O, 400 MHz): δ 7.85 (s, 1H, H8), 6.56 (br. s, 1H, H3′), 5.29–5.27 (m, 1H, H4′), 4.75–4.72 (m, 1H, H1′), 3.87–3.76 (m, 2H, OCH_2P), 3.07 (dt, *J* = 14.5, 7.9 Hz, 1H, H5′a), 2.15 (dt, *J* = 14.3, 4.6 Hz, 1H, H5′b). ^{13}C NMR (D_2O, 100 MHz): δ 159.0 (Cq), 153.8 (Cq), 151.2 (Cq), 140.9 (C3′), 138.3 (C8), 116.2 (Cq), 103.0 (Cq), 88.6 (d, *J* = 11.8 Hz, C1′), 65.5 (d, *J* = 156.6 Hz, OCH_2P), 58.4 (C4′), 37.0 (C5′). ^{31}P NMR (D_2O, 162 MHz): δ 15.3. MS (ESI^+): *m/z* = 454 $(M + H)^+$. UV (EtOH 95) λ_{max} = 252 nm (ε_{max} = 15400). HRMS (ESI^+): calcd. for $C_{11}H_{14}IN_5O_5P$ $[M+H]^+$ 453.9777; found 453.9756.

4.1.21. (±)-4-{[tert-butyl(dimethyl)silyl]oxy}-3-iodo-2-cyclopenten-1-yl)-6-methoxy-9H-purine (**21**)

To a stirred solution of (±) **16** (2.51 g, 7.0 mmol) and imidazole (1.43 g, 21.0 mmol) in DMF (10 mL) at 0 °C under an argon atmosphere was added portionwise TBDMSCl (4.22 g, 28.0 mmol). The mixture was stirred at rt for 12 h before concentration *in vacuo*. Purification by silica gel chromatography with petroleum ether/AcOEt (7/3) gave (±) **21** (2.99 g, 6.3 mmol, 87%) as a white foam. Rf = 0.20 (30% AcOEt in petroleum ether). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.50 (s, 1H, H2), 8.10 (s, 1H, H8), 6.33 (d, *J* = 2.4 Hz, 1H, H2′), 5.58–5.54 (m, 1H, H1′), 4.73 (dd, *J* = 6.8, 3.2 Hz, 1H, H4′), 4.16 (s, 3H, OCH_3), 2.99 (ddd, *J* = 14.8, 8.1, 7.0 Hz, 1H, H5′a), 1.91 (dt, *J* = 14.1, 3.5 Hz, 1H, H5′b), 0.90 (s, 9H, *t*-Bu), 0.19 (s, 3H, CH_3), 0.08 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.1 (Cq), 152.1 (C2), 151.5 (Cq), 140.9 (C8), 138.5 (C2′), 121.5 (Cq), 108.9 (C3′), 80.7 (C4′), 57.8 (C1′), 54,3 (OCH_3), 42.1 (C5′), 25.8 (3 × CH_3), 18.1 (Cq), −4.4 (CH_3), −4.6 (CH_3). MS (ESI^+): *m/z* = 473 $(M + H)^+$. UV (EtOH 95) λ_{max} = 249 nm (ε_{max} = 14500). HRMS (ESI^+): calcd. for $C_{17}H_{26}IN_4O_2Si$ $[M+H]^+$ 473.0870; found 473.0866.

4.1.22. (±)-2-fluoro-4-(6-methoxy-9H-purin-9-yl)-2-cyclopenten-1-ol (**22**) and (±)-4-(6-methoxy-9H-purin-9-yl)-2-cyclopenten-1-ol (**23**)

To a stirred solution of (±) **21** (2.81 g, 5.9 mmol) and NFSI (3.00 g, 9.5 mmol) in dry THF (60 mL) at −78 °C under an argon atmosphere, was added dropwise *n*-BuLi (2.5 M in hexane, 9.52 mL, 23.8 mmol). After stirring at −78 °C for 45 min, saturated NH_4Cl was added and the mixture was warmed to rt. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried (MgSO4), filtered, and concentrated. The residue was purified by silica gel chromatography with petroleum ether/AcOEt (6/4) to give an inseparable mixture of the fluorinated and dehalogenated compounds. This mixture was diluted in dry THF (61 mL) and a 1 M solution of TBAF (4.4 mL, 4.4 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then concentrated *in vacuo*. The residual oil was chromatographed with a stepwise gradient of CH_3OH (0–10%) in AcOEt to afford (±) **22** (311 mg, 1.2 mmol, 21%) as a white foam and (±) **23** (450 mg, 1.9 mmol, 33%) as a white solid. Compound (±) **22**: Rf = 0.31 (5% CH_3OH in AcOEt). ^1H NMR ($CDCl_3$, 300 MHz): δ 8.47 (s, 1H, H2), 7.96 (s, 1H, H8), 5.35–5.29 (m, 1H, H4′), 5.23 (d, *J* = 2.5 Hz, 1H, H3′), 4.64 (d, *J* = 7.1 Hz, 1H, H1′), 4.16 (s, 3H, OCH_3), 3.17–3.06 (m, 1H, H5′a), 2.29 (dd, 1H, *J* = 15.6, 1.9 Hz, 1H, H5′b). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4 (d, *J* = 290.4 Hz, C2′), 161.4 (Cq), 151.4 (C2), 150.6 (Cq), 142.1 (C8), 123.0 (Cq), 104.2 (d, *J* = 12.5 Hz, C3′), 70.2 (d, *J* = 22.1 Hz, C1′), 55.1 (d, *J* = 11.6 Hz, C4′), 54.4 (OCH_3), 38.0 (d, *J* = 5.7 Hz, C5′). ^{19}F NMR (282 MHz, $CDCl_3$): δ 122.7 (m). MS (ESI^+): *m/z* = 251 $(M + H)^+$. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 10300). HRMS (ESI^+): calcd. for $C_{11}H_{12}FN_4O_2$ $[M+H]^+$ 251.0944; found 251.0952. Compound (±) **23**: Rf = 0.28 (5% CH_3OH in AcOEt). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.44 (s, 1H, H2), 7.96 (s, 1H, H8), 6.34–6.31 (m, 1H, H3′), 6.06 (br s, 1H, OH), 5.82 (dd, *J* = 5.5, 2.5 Hz, 1H, H2′), 5.37–5.33 (m, 1H, H4′), 4.85 (br s, 1H, H1′), 4.15 (s, 3H, OCH_3), 2.98 (ddd, *J* = 15.6, 9.1, 7.7 Hz, 1H, H5′a), 2.19 (d, *J* = 15.4, 1H, H5′b). NMR ($CDCl_3$, 100 MHz): δ 161.4 (Cq), 151.2 (C2), 150.7 (Cq), 142.3 (C8), 140.0 (C3′), 129.8 (C2′), 122.9 (Cq), 75.2 (C1′), 60.2 (C4′), 54.3 (OCH_3), 39.6 (C5′). MS (ESI^+): *m/z* = 233 $(M + H)^+$. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 10500). HRMS (ESI^+): calcd. for $C_{11}H_{13}N_4O_2$ $[M+H]^+$ 233.1039; found 233.1039.

4.1.23. (±)-diethyl {[-2-fluoro-4-(6-methoxy-9H-purin-9-yl)-2-cyclopenten-1-yl]oxy}methylphosphonate (**24**)

Compound (±) **24** (yellow oil, 422 mg, 88%) was synthesized from (±) **22** (300 mg, 1.2 mmol) using a similar procedure as described for (±) **14** but lasting for 12 days. Rf = 0.21 (5% CH_3OH in AcOEt). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H, H2), 8.11 (s, 1H, H8), 5.64–5.59 (m, 1H, H4′), 5.48 (d, *J* = 2.7 Hz, 1H, H3′), 4.57 (dd, *J* = 7.4, 1.8 Hz, 1H, H1′), 4.19–4.09 (m, 4H, 2 × CH_2), 4.15 (s, 3H, OCH_3), 4.00 and 3.88 (ABX, *J* = 13.8, 8.9 Hz, 2H, CH_2), 3.03 (dt, *J* = 15.3, 7.8 Hz, 1H, H5′a), 2.05 (br dd, *J* = 15.1, 2.3 Hz, 1H, H5′b), 1.31 (t, *J* = 7.1 Hz, 3H, CH_3), 1.29 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.1 (d, *J* = 289.9 Hz, C2′), 161.1 (Cq), 152.1 (C2), 151.5 (Cq), 140.7 (C8), 121.6 (Cq), 107.3 (d, *J* = 11.7 Hz, C3′), 79.0 (dd, 1H, *J* = 20.5, 11.1 Hz, C1′), 64.2 (d, *J* = 167.3 Hz, OCH_2P), 62.7 (d, *J* = 6.5 Hz, 2 × CH_2), 54.2 (OCH_3), 51.5 (d, *J* = 10.8 Hz, C4′), 37.3 (d, *J* = 4.9 Hz, CH_2), 16.5 (d, *J* = 5.4 Hz, 2 × CH_3). ^{31}P NMR (D_2O, 162 MHz): δ 19.8 ppm. ^{19}F NMR ($CDCl_3$, 375.6 MHz): δ −119.7 (t, *J* = 2.7 Hz). MS (ESI^+): *m/z* = 401 $(M + H)^+$. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 12000). HRMS (ESI^+): calcd. for $C_{16}H_{23}FN_4O_5P$ $[M+H]^+$ 401.1390; found 401.1388.

4.1.24. (±)-disodium {[-2-fluoro-4-(6-oxo-1,6-dihydro-9H-purin-9-yl)-2-cyclopenten-1-yl]oxy}methylphosphonic acid (**25**)

Compound (±) **25** (white solid, 228 mg, 70%) was synthesized from (±) **24** (350 mg, 0.9 mmol) using the similar procedure as described for (±) **15** with TMSBr (20 eq.) and stirred for 36 h. Rf = 0.23 (isopropanol/NH_4OH/H_2O: 7/2/1). ^1H NMR (D_2O, 300 MHz): δ 8.20 (s, 1H, H2), 8.13 (s, 1H, H8), 5.65 (d, *J* = 2.6 Hz, 1H, H3′), 5.50–5.43 (m, 1H, H4′), 4.70 (dd, *J* = 7.6, 3.1 Hz, 1H, H1′), 3.69 (d, *J* = 9.4 Hz, 2H, OCH_2P), 3.10 (dt, *J* = 15.1, 7.9 Hz, 1H, H5′a), 2.10–2.02 (m, 1H, H5′b). ^{13}C NMR (D_2O, 75 MHz): δ 164.5 (d, *J* = 286.4 Hz, C2′), 158.5 (Cq), 148.2 (Cq), 145.6 (C2), 140.5 (C8), 123.4 (Cq), 106.7 (d, *J* = 13.0 Hz, C3′), 78.4 (dd, *J* = 20.5, 12.3 Hz, C1′), 65.9 (d, *J* = 155.2 Hz, 2H, OCH_2P), 52.4 (d, *J* = 11.5 Hz, C4′), 36.0 (d, *J* = 5.4 Hz, C5′). ^{31}P NMR (121 MHz, D_2O): δ 14.9. ^{19}F NMR (282 MHz, D_2O): δ −121.8 (d, *J* = 5.5 Hz). MS (ESI^+): *m/z* = 331 $(M + H)^+$. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 8500). HRMS (ESI^+): calcd. for

$C_{11}H_{13}FN_4O_5P$ $[M+H]^+$ 331.0608; found 331.0617.

*4.1.25. (±)-tert-butyl[(-4-{[tert-butyl(diphenyl)silyl]oxy}-3-iodo-2-cyclopenten-1-yl)oxy]dimethylsilane (**26**)*

To a stirred solution of (±) **3** (4.01 g, 11.8 mmol) and imidazole (2.41 g, 35.4 mmol) in dry DMF (40 mL) at 0 °C under an argon atmosphere, was added portionwise TBDPSCl (4.52 mL, 17.7 mmol). The reaction mixture was stirred at rt for 48 h and poured onto a solution of saturated NH_4Cl (50 mL) and CH_2Cl_2 (50 mL) at 0 °C. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with $NaHCO_3$, water and brine then dried, filtered, and concentrated *in vacuo*. Purification by column chromatography with petroleum ether/AcOEt (99/1) gave (±) **26** (6.74 g, 11.6 mmol, 98%) as a colorless oil. Rf = 0.74 (20% AcOEt in petroleum ether). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.80–7.70 (m, 4H, ArH), 7.44–7.35 (m, 6H, ArH), 6.20 (t, J = 1.7 Hz, 1H, H2), 4.49 (t, J = 6.6 Hz, 1H, H4), 4.40–4.36 (m, 1H, H1), 2.18 (dt, J = 12.7, 7.0 Hz, 1H, H5a), 1.64 (dt, J = 12.7, 6.1 Hz, 1H, H5b), 1.12 (s, 9H, *t*-Bu), 0.85 (s, 9H, *t*-Bu), −0.01 (s, 3H, CH_3), −0.02 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.3 (C3), 136.5 (2 × CAr), 136.2 (2 × CAr), 134.2 (Cq), 133.3 (Cq), 129.8 (CAr), 129.8 (CAr), 127.6 (4 × CAr), 105.8 (C2), 79.2 (C1), 75.5 (C4), 44.4 (C5), 27.2 (3 × CH_3), 25.9 (3 × CH_3), 19.5 (Cq), 18.2 (Cq), −4.6 (CH_3), −4.6 (CH_3). MS (ESI>0): m/z = 579.2 $[M+H]^+$.

*4.1.26. (±)-tert-butyl[(-4-{[tert-butyl(diphenyl)silyl]oxy}-3-fluoro-2-cyclopenten-1-yl)oxy]dimethylsilane (**27**)*

To a stirred solution of (±) **26** (5.05 g, 8.7 mmol) and NFSI (4.40 g, 13.9 mmol) in dry THF (60 mL) at −78 °C under an argon atmosphere, was added dropwise *n*-BuLi (2.5 M in hexane, 14 mL, 35.0 mmol). After stirring at −78 °C for 2 h, saturated NH_4Cl was added and the mixture was warmed to rt. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried (MgSO4), filtered, and concentrated to give a mixture of compound (±) **27** and its dehalogenated derivative (±) **28**. This mixture was used in the next step without further purification. A part of the residue was purified by silica gel chromatography with a stepwise gradient of CH_2Cl_2 (10–15%) in petroleum ether to afford compound (±) **27**. Rf = 0.53 (30% CH_2Cl_2 in petroleum ether). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.74–7.69 (m, 4H, ArH), 7.46–7.36 (m, 6H, ArH), 5.20 (d, J = 1.4 Hz, 1H, H2), 4.52–4.42 (m, 2H, H1+H4), 2.50–2.41 (m, 1H, H5a), 1.79–1.71 (m, 1H, H5b), 1.09 (s, 9H, *t*-Bu), 0.90 (s, 9H, 3 × CH_3), 0.07 (s, 3H, CH_3), 0.06 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.5 (d, J = 287.0 Hz, C2), 136.0 (CAr), 136.0 (CAr), 135.9 (CAr), 134.0 (Cq), 133.5 (Cq), 129.8 (3 × CAr), 127.7 (4 × CAr), 109.2 (d, J = 6.8 Hz, H3), 70.6 (d, J = 20.3 Hz, C1), 68.6 (d, J = 11.9 Hz, C4), 43.8 (d, J = 4.9 Hz, C5), 26.9 (s, 3 × CH_3), 26.0 (s, 3 × CH_3), 19.3 (Cq), 18.2 (Cq), −4.5 (2 × CH_3). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −126.52 (d, J = 6.7 Hz). MS (ESI^+): m/z = 471 $(M + H)^+$. HRMS (ESI^+): calcd. for $C_{27}H_{40}FO_2Si_2$ $[M+H]^+$ 471.2551; found: 471.2563.

*4.1.27. (±)-4-{[tert-butyl(diphenyl)silyl]oxy}-3-fluoro-2-cyclopenten-1-ol (**29**)*

To a stirred solution of crude mixture (±) **27** and (±) **28** (4.56 g) in CH_3OH (80 mL) at 0 °C was added *p*-TsOH, 231 mg, 1.2 mmol). The reaction mixture was stirred at rt for 1 h and volatiles were evaporated to dryness. The residue was poured onto a solution of CH_2Cl_2 and saturated $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography with a stepwise gradient of AcOEt (10–20%) in petroleum ether gave (±) **29** (1.8 g, 57% over two steps) as a colorless oil and (±) **30** (650 mg, 22% over two steps). Compound (±) **29**. Rf = 0.29 (20% AcOEt in petroleum ether). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.72–7.67 (m, 4H, ArH), 7.47–7.36 (m, 6H, ArH), 5.31 (d, J = 2.4 Hz, 1H, H2), 4.54–4.50 (m, 1H, H4), 4.46–4.40 (m, 1H, H1), 2.51 (dt, J = 14.3, 7.3 Hz, 1H, H5a), 1.72–1.64 (m, 1H, H5b), 1.09 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.8 (d, J = 288.7 Hz, C3), 136.0 (CAr), 135.9 (2 × CAr), 133.7 (Cq), 133.2 (Cq), 130.0 (CAr), 129.9 (CAr), 127.8 (2 × CAr), 127.7 (2 × CAr), 109.0 (d, J = 7.2 Hz, C2), 70.9 (d, 7H, J = 20.8 Hz, C4), 69.1 (d, J = 10.9 Hz, C1), 43.3 (d, J = 5.0 Hz, C5), 26.9 (3 × CH_3), 19.2 (Cq). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −124.8 (dt, J = 6.6, 1.9 Hz). MS (ESI^+): m/z = 355 $(M-H)^-$. HRMS (ESI^+): calcd. for $C_{21}H_{24}FO_2Si$ $[M-H]^-$ 355.1530; found: 355.1549. The physicochemical properties of compound (±) **30** were similar to those previously reported [17].

*4.1.28. (±)-9-((1S,4S)-4-{[tert-butyl(diphenyl)silyl]oxy}-3-fluoro-2-cyclopenten-1-yl)-6-chloro-9H-purine (**31**)*

To a stirred solution of PPh_3 (4.24 g, 16.2 mmol) and 6-chloropurine (2.50 g, 16.2 mmol) in dry THF (110 mL) at 0 °C was added dropwise DIAD (3.2 mL, 16.2 mmol) under an argon atmosphere. The mixture was stirred at rt for 1 h then a solution of (±) **29** (1.80 g, 5.1 mmol) in dry THF (30 mL) was added and stirred at rt for 1 h. The precipitate was filtrated through a pad of Celite, the filtercake was washed with Et_2O and the filtrate was concentrated *in vacuo*. Purification by silica gel chromatography with CH_2Cl_2/AcOEt (95/5) afforded (±) **31** as a white foam (1.34 g, 54%). Rf = 0.30 (5% AcOEt in CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.67 (s, 1H, H2), 7.96 (s, 1H, H8), 7.70–7.65 (m, 4H, ArH), 7.48–7.35 (m, 6H, ArH), 5.81–5.76 (m, 1H, H1′), 5.39 (d, 1H, J = 2.3 Hz, H2′), 5.11 (br d, J = 2.5 Hz, 1H, H4′), 2.60 (ddd, 1H, J = 14.4, 8.3, 3.8 Hz, H5′a), 2.16 (ddd, 1H, J = 14.4, 7.2, 2.6 Hz, H5′b), 1.10 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3 (d, J = 291.8, C3′), 152.0 (C2), 151.4 (Cq), 151.3 (Cq), 143.1 (C8), 135.9 (CAr), 135.9 (CAr), 133.3 (Cq), 132.8 (Cq), 132.2 (Cq), 130.2 (CAr), 130.2 (CAr), 128.0 (CAr), 127.9 (CAr), 104.1 (d, J = 13.3 Hz, C2′), 72.0 (d, J = 20.3 Hz, C4′), 54.5 (d, J = 12.1 Hz, C1′), 40.7 (d, J = 5.1 Hz, C5′), 26.9 (3 × CH_3), 19.3 (Cq). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −118.1. UV (EtOH 95) λ_{max} = 265 nm (ε_{max} = 8000). MS (ESI^+): m/z = 493 $(M + H)^+$. HRMS (ESI^+): calculated for $C_{26}H_{27}ClFN_4OSi$ $[M+H]^+$ 493.1627; found: 493,1618.

*4.1.29. (±)-N′-{9-[(1S,4S)-3-fluoro-4-hydroxy-2-cyclopenten-1-yl]-9H-purin-6-yl}-N,N-dimethylimidoformamide (**33**)*

A solution of (±) **31** (1.2 g, 2.6 mmol) in methanolic ammonia (2 M, 100 mL) was heated at 70 °C in a stainless-steel Parr high pressure reactor for 30 h. The mixture was filtered, the solid was washed with CH_3OH and the filtrate was concentrated *in vacuo*. The residue was partially purified by silica gel chromatography with a stepwise gradient of CH_3OH (5–10%) in CH_2Cl_2. This residue was used in the next step without further purification. Rf = 0.19 (10% CH_3OH in CH_2Cl_2). MS (ESI>0): m/z = 236 $[M+H]^+$. This residue was converted into compound (±) **33** (colourless oil, 528 mg, 70%) using the similar procedure as described for (±) **10** with heating at 50 °C overnight and purified with a stepwise gradient of CH_3OH (0–10%) in CH_2Cl_2. Rf = 0.26 (10% CH_3OH in CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.92 (s, 1H, H2), 8.51 (s, 1H, H8), 7.84 (s, 1H, NCH=N), 5.78–5.73 (m, 1H, H1′), 5.41 (d, 1H, J = 2.5 Hz, H2′), 5.18 (br s, 1H, H4′), 4.08 (br s, 1H, OH), 3.24 (s, 3H, CH_3), 3.19 (s, 3H, CH_3), 2.61 (ddd, 1H, J = 13.8, 8.1, 3.8 Hz, H5′a), 2.45 (ddd, 1H, J = 14.6, 7.5, 2.9 Hz, H5′b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.8 (d, J = 289.2 Hz, C3′), 159.7 (Cq), 158.2 (C2), 152.6 (C8), 151.4 (Cq), 139.4 (CH=N), 126.4 (Cq), 104.8 (d, J = 12.1 Hz, C2′), 70.3 (d, J = 2.0 Hz, C4′), 53.6 (d, J = 12.1 Hz, C1′), 41.3 (CH_3), 40.2, (d, J = 5.2 Hz, C5′), 35.2 (CH_3). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −122.0. UV (EtOH 95) λ_{max} = 310 nm (ε_{max} = 15000). MS (ESI^+): m/z = 291 $(M + H)^+$. HRMS (ESI^+): calculated for $C_{13}H_{16}FN_6O$ $[M+H]^+$ 291.1370; found 291.1367.

*4.1.30. (±)-N′-{9-[(1S,4R)-3-fluoro-4-hydroxy-2-cyclopenten-1-yl]-9H-purin-6-yl}-N,N-dimethylimidoformamide (**34**)*

To a solution of PPh_3 (2.49 g, 9.5 mmol) and BzOH (1.16 g, 9.5 mmol) in dry THF (10 mL) at rt was cannulated a solution of (±)

33 (553 mg, 1.9 mmol) in dry THF (10 mL). The reaction mixture was cooled down to 0 °C and DIAD (1.87 mL, 9.5 mmol) was added dropwised. The reaction mixture was stirred at rt for 3 h and volatiles were evaporated to dryness. The residue was dissolved in CH_3OH (38 mL) and anhydrous K_2CO_3, (524 mg, 3.8 mmol) was added. The reaction mixture was stirred at rt for 2 h then concentrated to dryness. Purification by silica gel chromatography with a stepwise gradient of CH_3OH (0–10%) in CH_2Cl_2 afforded (±) **34** (472 mg, 85%) as a colourless oil. Rf = 0.45 (10% CH_3OH in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.94 (s, 1H, H2), 8.47 (s, 1H, H8), 7.88 (s, 1H, CH=N), 7.33 (br s, 1H, OH), 5.27–5.23 (m, 1H, H1′), 5.21 (d, 1H, *J* = 2.6 Hz, H2′), 4.62 (d, *J* = 7.4 Hz, 1H, H4′), 3.26 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 3.13–3.05 (m, 1H, H5′a), 2.35 (dd, *J* = 15.6, 2.3 Hz, 1H, H5′b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6 (d, *J* = 290.2 Hz, C3′), 160.2 (Cq), 158.4 (C2), 151.6 (C8), 150.3 (Cq), 141.7 (CH=N), 127.7 (Cq), 104.2 (d, *J* = 12.2 Hz, C2′), 70.4 (d, *J* = 22.2 Hz, C4′), 55.3 (d, *J* = 11.5 Hz, C1′), 41.5 (CH_3), 37.9 (d, *J* = 5.7 Hz, C5′), 35.4 (CH_3). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −123.2. UV (EtOH 95) λ_{max} = 312 nm (ε_{max} = 23400). MS (ESI^+): *m/z* = 291.1 $(M + H)^+$. HRMS (ESI^+): calculated for $C_{13}H_{16}N_6OF$ $[M+H]^+$ 291.1370; found: 291.1369.

*4.1.31. (±)-diethyl {[(1R,4S)-4-(6-amino-9H-purin-9-yl)-2-fluoro-2-cyclopenten-1-yl]oxy}methylphosphonate (**35**)*

Compound (±) **35** (yellow oil, 187 mg, 71%) was synthesized from (±)-**34** (198 mg, 0.7 mmol) using the similar procedure as described for (±) **11** with 3 eq. of LiO*t*Bu, 4 eq. of diethyl *p*-toluene sulfonyloxymethyl phosphonate and stirred for 3 days at rt. Rf = 0.46 (10% CH_3OH in CH_2Cl_2). ^{1}H NMR (300 MHz, MeOD): δ 8.21 (s, 1H, H2), 8.16 (s, 1H, H8), 5.69 (d, *J* = 2.5 Hz, 1H, H3′), 5.57–5.53 (m, 1H, H4′), 4.87 (s, 2H, NH_2), 4.65 (dd, *J* = 7.0, 1.8 Hz, 1H, H1′), 4.21–4.01 (m, 6H, 2xCH_2), 3.06 (dt, *J* = 15.2, 7.7 Hz, 1H, H5′a), 2.09 (dd, *J* = 15.0, 2.2 Hz, 1H, H5′b), 1.34–1.28 (m, 6H, 2xCH_3). ^{13}C NMR (75 MHz, MeOD): δ 166.2 (d, *J* = 287.2 Hz, C2′), 157.3 (Cq), 153.8 (C2), 150.2 (Cq), 140.7 (C8), 120.2 (Cq), 108.5 (d, *J* = 12.5 Hz, C3′), 80.7 (dd, *J* = 21.0, 13.7 Hz, C1′), 64.3 (d, *J* = 167.8 Hz, OCH_2P), 64.2 (d, *J* = 6.6 Hz, 2x$\underline{C}H_2CH_3$), 53.3 (d, *J* = 11.2 Hz, C4′), 37.8 (d, *J* = 5.3 Hz, C5′), 16.74 (d, *J* = 5.7 Hz, 2xCH_3). ^{31}P NMR (121 MHz, MeOD): δ 21.4. ^{19}F NMR (282 MHz, MeOD): δ −123.2 (d, *J* = 2.5 Hz). UV (EtOH 95) λ_{max} = 262 nm (ε_{max} = 13520). MS (ESI^+): *m/z* = 386 $(M + H)^+$. HRMS (ESI^+): calculated for $C_{15}H_{22}FN_5O_4P$ $[M+H]^+$ 386.1393; found 386.1405.

*4.1.32. (±)-disodium-{[(1R,4S)-4-(6-amino-9H-purin-9-yl)-2-fluoro-2-cyclopenten-1-yl]oxy}methylphosphonic acid (**36**)*

Compound (±) **36** (white solid, 32 mg, 42%) was synthesized from (±) **35** (79 mg, 0.2 mmol) using the similar procedure as described for (±) **15**. Rf = 0.19 (iPrOH/NH_4OH/H_2O: 7/2/1). ^{1}H NMR (400 MHz, D_2O): δ 8.12 (s, 1H, H2), 8.02 (s, 1H, H8), 5.62 (d, *J* = 2.5 Hz, 1H, H3′), 5.34–5.32 (m, 1H, H4′), 4.67 (dd, *J* = 7.4, 2.7 Hz, 1H, H1′), 3.74–3.65 (m, 2H, OCH_2P), 3.05 (dt, *J* = 15.5, 7.9 Hz, 1H, H5′a), 1.96 (br d, *J* = 14.9 Hz, 1H, H5′b). ^{13}C NMR (100 MHz, D_2O): δ 164.6 (d, *J* = 286.2 Hz, C2′), 155.1 (Cq), 152.1 (C2), 148.1 (Cq), 140.6 (C8), 118.4 (Cq), 106.8 (d, *J* = 13.3 Hz, C3′), 78.7 (dd, *J* = 20.3, 12.7 Hz, C1′), 65.8 (d, *J* = 156.2 Hz, OCH_2P), 52.07 (d, *J* = 11.4 Hz, C4′), 36.1 (C5′). ^{31}P NMR (162 MHz, D_2O): δ 15.0. ^{19}F NMR (D_2O, 376.5 MHz): δ −121.6. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 10300). MS (ESI^+): *m/z* = 330 $(M + H)^+$. HRMS (ESI^+): calculatedd for $C_{11}H_{14}FN_5O_4P$ $[M+H]^+$ 330.0767 found 330.0743.

*4.1.33. (±)-9-((1S,4S)-4-{[tert-butyl(diphenyl)silyl]oxy}-3-fluoro-2-cyclopenten-1-yl)-6-chloro-9H-purin-2-amine (**32**)*

To a stirred solution of 2-amino-6-chloro-9*H*-purine (553 mg, 3.3 mmol) and PPh_3 (856 mg, 3.3 mmol) in dry THF (240 mL), at 0 °C under argon atmosphere, was added dropwise DIAD (640 μL, 3.3 mmol) over 5 min. After stirring for 1 h a solution of (±)-**29** (529 mg, 1.5 mmol) in dry THF (11 mL) was added, and stirred at rt for 4 h. The solution was concentrated *in vacuo* and the resulting syrup was filtered through a pad of Celite. Purification by silica gel chromatography with a stepwise gradient of AcOEt (20–30%) in petroleum ether gave (±) **32** as a white foam (396 mg, 0.8 mmol, 52%). Rf = 0.18 (30% AcOEt in petroleum ether). Rf = 0.31 (30% AcOEt in petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70–7.65 (m, 4H, ArH), 7.60 (s, 1H, H8), 7.48–7.36 (m, 6H, ArH), 5.55–5.51 (m, 1H, H1′), 5.31 (d, 1H, *J* = 2.3 Hz, H2′), 5.11 (br s, 1H, H4′), 4.96 (s, 2H, NH_2), 2.53 (ddd, 1H, *J* = 14.3, 8.3, 3.9 Hz, H5′a), 2.15 (ddd, 1H, *J* = 14.3, 7.2, 2.4 Hz, H5′b), 1.10 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.8 (d, *J* = 290.9 Hz, C3′), 158.9 (Cq), 153.2 (Cq), 151.3 (Cq), 140.3 (C8), 135.9 (2 × CAr), 135.8 (2 × CAr), 133.3 (Cq), 132.8 (Cq), 130.1 (2 × CAr), 127.9 (2 × CAr), 127.8 (2 × CAr), 125.6 (Cq), 104.2 (d, *J* = 12.8 Hz, C2′), 72.1 (d, *J* = 20.3 Hz, C4′), 53.7 (d, *J* = 12.0 Hz, C1′), 40.3 (d, *J* = 4.9 Hz, C5′), 26.8 (3 × CH_3), 19.3 (Cq). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −119.2. UV (EtOH 95) λ_{max} = 311 nm (ε_{max} = 6200). MS (ESI^+): *m/z* = 508 $(M + H)^+$. HRMS (ESI^+): calculated for $C_{26}H_{28}ClFN_5OSi$ $[M+H]^+$ 508.1736; found 508.1731.

*4.1.34. (±)-(1S,4S)-4-(2-Amino-6-methoxy-9H-purin-9-yl)-2-fluoro-2-cyclopenten-1-ol (**37**)*

To a stirred solution of (±) **32** (96 mg, 0.2 mmol) in CH_3OH (1.9 mL) was added anhydrous K_2CO_3 (262 mg, 1.9 mmol). The reaction mixture was heated at reflux for 4 h and was concentrated *in vacuo*. Purification by silica gel chromatography with a stepwise gradient of CH_3OH (0–10%) in CH_2Cl_2 afforded (±) **37** (40 mg, 80%) as a white solid. Rf = 0.22 (5% CH_3OH in CH_2Cl_2). ^{1}HNMR (DMSO-d6, 400 MHz): δ 7.83 (s, 1H, H8), 6.41 (s, 1H, NH_2), 5.59 (d, 1H, *J* = 6.3 Hz, OH), 5.49–5.47 (m, 2H, H3′ and H4′), 4.99 (m, 1H, H1′), 3.95 (s, 3H, OCH_3), 2.37 (ddd, 1H, *J* = 14.0, 7.6, 2.7, H5′a), 2.31–2.24 (m, 1H, H5′b). ^{13}C NMR (DMSO-d6, 100 MHz): δ 166.5 (d, *J* = 286.4 Hz, C2′), 160.6 (Cq), 159.7 (Cq), 153.7 (Cq), 137.8 (C8), 114.1 (Cq), 105.1 (d, *J* = 12.1 Hz, C3′), 69.1 (d, *J* = 21.1 Hz, C1′), 53.1 (OCH_3), 52.4 (d, *J* = 12.8 Hz, C4′), C5′ signal in DMSO peak. ^{19}F NMR (DMSO-d6, 376.5 MHz): δ −124.0. UV (EtOH 95) λ_{max} = 250 nm (ε_{max} = 11100), λ_{max} = 282 nm (ε_{max} = 11900). MS (ESI^+): *m/z* = 266.1 $(M + H^+)$. HRMS (ESI^+): calculatedd for $C_{11}H_{13}N_5O_2F$ $[M+H]^+$ 266.1053; found: 266.1052.

*4.1.35. (±)-(1R,4S)-4-(2-Amino-6-methoxy-9H-purin-9-yl)-2-fluoro-2-cyclopenten-1-ol (**38**)*

To a stirred suspension of PPh_3 (1.28 g, 4.9 mmol) and BzOH (598 mg, 4.9 mmol) in dry THF (6 mL) under an argon atmosphere was added a solution of (±) **37** (260 mg, 1.0 mmol) in dry THF (6 mL) at rt. The mixture was cooled to 0 °C and DIAD (965 μL, 4.9 mmol) was added dropwise. The reaction mixture was stirred at rt for 2.5 h and then concentrated to dryness. The residue was dissolved in CH_3OH (18 mL) and anhydrous K_2CO_3 (276 mg, 2.0 mmol) was added. The solution was stirred at rt for 16 h and concentrated *in vacuo*. Purification by flash chromatography on silica gel with a stepwise gradient of CH_3OH (0–6%) in CH_2Cl_2 afforded (±) **38** (240 mg, 93%) as a white foam. Rf = 0.38 (5% CH_3OH in CH_2Cl_2) ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (s, 1H, H8), 7.28–7.26 (m, 1H, OH), 5.19 (d, 1H, *J* = 2.6 Hz, H3′), 5.15–5.12 (m, 1H, H4′), 4.97 (s, 2H, NH_2), 4.57 (t, *J* = 8.4 Hz, 1H, H1′), 4.05 (s, 3H, OCH_3), 3.07–2.99 (m, 1H, H5′a), 2.24 (dd, *J* = 15.5, 2.2 Hz, 1H, H5′b). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3 (d, *J* = 289.8 Hz, C2′), 162.1 (Cq), 158.6 (Cq), 152.2 (Cq), 139.4 (C8), 117.2 (Cq), 104.3 (d, *J* = 12.1 Hz, C3′), 70.3 (d, *J* = 22.3 Hz, C1′), 54.8 (d, *J* = 11.6 Hz, C4′), 54.1 (OCH_3), 38.0 (d, *J* = 5.7 Hz, C5′). ^{19}F NMR ($CDCl_3$, 376.5 MHz): δ −123.6. UV (EtOH 95) λ_{max} = 282 nm (ε_{max} = 6500). MS (ESI^+): *m/z* = 266 $(M + H)^+$. HRMS (ESI^+): calculatedd for $C_{11}H_{13}FN_5O_2$ $[M+H]^+$ 266.1053; found 308.1164.

*4.1.36. (±)-disodium-{[(1R,4S)-4-(2-amino-6-oxo-1,6-dihydro-9H-purin-9-yl)-2-fluoro-2-cyclopenten-1-yl]oxy}methylphosphonic acid (**39**)*

To a stirred solution of alcohol (±) **38** (99 mg, 0.4 mmol) in dry THF (5 mL) at 0 °C under an argon atmosphere was added LiO*t*Bu (2.2 M solution in THF, 0.545 μL, 1.2 mmol). The solution was stirred at 0 °C for 1 h until addition of diethyl *p*-toluene sulfonyloxymethyl phosphonate (516 mg, 1.6 mmol). The reaction mixture was stirred at rt for 3 days, and then quenched by addition of AcOH (few drops). Concentration to dryness followed by purification by silica gel chromatography with a stepwise gradient of CH_3OH (2–10%) in AcOEt gave an inseparable mixture of phosphonate derivative and hydroxymethylphosphonic acid. This mixture was used in the next step without further purification. Rf = 0.23 (10% CH_3OH in AcOEt). MS (ESI^+): *m/z* = 416.1 $(M + H)^+$. To a stirred solution of contaminated phosphonate derivative (239 mg) in dry DMF (5 mL) at 0 °C was added dropwise TMSBr (1.2 mL, 9.3 mmol) under an argon atmosphere. The reaction mixture was stirred at rt for 16 h then neutralized with an aqueous triethylamonium hydrogen bicarbonate solution (1 M, pH 7) and concentrated to dryness under reduce pressure. Purification by flash chromatography on silica gel with a stepwise gradient of iPrOH/NH_4OH/H_2O (7/2/1 to 9/9/1) followed by reverse-phase column chromatography with H_2O/CH_3OH (100/0 to 80/20), ion exchange on Dowex 50WX2 (Na^+ form) and freeze-drying gave (±) **39** (34 mg, 23% over 2 steps) as a white solid. Rf = 0.10 (iPrOH/NH_4OH/H_2O: 7/2/1). ^1H NMR (D_2O, 400 MHz): δ 7.76 (s, 1H, H8), 5.51 (d, 1H, *J* = 2.5 Hz, H3′), 5.18–5.14 (m, 1H, H4′), 4.62 (dd, 1H, *J* = 7.6, 3.3 Hz, H1′), 3.53–3.43 (m, 2H, OCH_2P), 2.99 (dt, *J* = 15.6, 8.0 Hz, 1H, H5′a), 1.90 (dd, *J* = 14.7, 1.8, 1H, H5′b). ^{13}C NMR (D_2O, 100 MHz): δ 168.3 (Cq), 164.1 (d, *J* = 285.1, C2′), 161.2 (Cq), 150.9 (Cq), 136.6 (C8), 117.7 (Cq), 107.1 (d, *J* = 12.2 Hz, C3′), 78.2 (dd, *J* = 19.9, 12.1, C1′), 67.1 (d, *J* = 150.1, CH_2P), 51.1 (d, *J* = 11.4 Hz, C4′), 36.3 (d, *J* = 5.0 Hz, C5′). ^{31}P NMR (D_2O, 162 MHz): δ 13.1.^{19}F NMR (D_2O, 376.5 MHz): δ −122.9. UV (EtOH 95) λ_{max} = 256 nm (ε_{max} = 9300). MS (ESI^+): *m/z* = 346.2 $(M + H)^+$. HRMS (ESI^+): calculated for $C_{11}H_{14}FN_5O_5P$ $[M+H]^+$ 346.0717; found: 346.0739.

4.2. Antiviral activity

4.2.1. Cells and virus

Peripheral blood mononuclear cells (PBMC) from healthy donors were isolated and stimulated for 3 days with 1 μg/mL of phytohemagglutinin-P (PHA-P, Sigma) and 5 IU/mL of recombinant human interleukin-2 (rHuIL-2, Roche). PBMC were growth under CO_2 in a humid atmosphere at 37 °C in RPMI-1640 glutamax medium supplemented with antibiotics (penicillin, streptomycin, néomycin), 10% fetal calf serum (FCS, previously inactivated by heat) and 10 UI/mL of rHuIL-2. The HIV-1 LAI strain was previously described [18].

4.2.2. Anti-HIV assay

PHA-P activated PBMCs (1.5×10^5 cells) were pre-treated for 30 min by increasing concentrations of the various compounds to be tested and then infected with 100% infectious tissue culture doses 50% ($TCID_{50}$) of the HIV-1-LAI. Supernatants were collected at day 7 post infection and stored at −20 °C. Viral replication was measured by quantifying reverse transcriptase activity in cell culture supernatants by the use of Lenti kit RT (Cavidi). Cytotoxicity of the compounds was evaluated in uninfected PHA-P PBMC by MTT assay (Promega) on day 7. Experiments were performed in triplicate and repeated with another blood donors. Data analyses were performed using SoftMax® Pro 4.6 sofware (Molecular Devices). Percent of inhibition of RT activity or cell viability were plotted *versus* compound concentration and fitted with quadratic curves to determine 50% effective concentration (EC_{50}) and 50% cytotoxic concentration (CC_{50}).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejmech.2018.03.038.

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