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Synthesis of an Anti-hepatitis B Agent, 2′-Fluoro-6′-Methylene-carbocyclic Adenosine (FMCA) and its Phosphoramidate (FMCAP)

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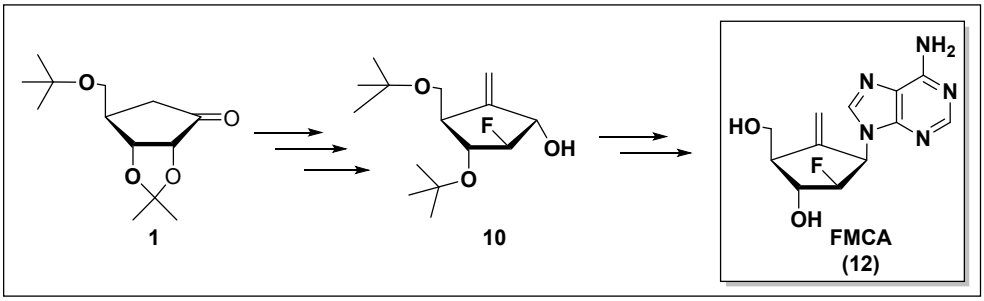


ABSTRACT

2′-Fluoro-6′-methylene-carbocyclic adenosine (FMCA, **12**) and its phosphoramidate prodrug (FMCAP, **14**) (Figure 1) has been proven as a potential anti-HBV agent against both adefovir-resistant as well as lamivudine-resistant double (rtL180M/rtM204V) mutants. Furthermore, *in vitro,* these agents have demonstrated significant activity against lamivudine/entecavir triple mutants (L180M+S202G+M204V). These preliminary results encourage us for further biological evaluation of FMCA and FMCAP to develop as a potential clinical candidate as an anti-HBV agent, which may overcome the problem of drug-resistance in HBV therapy. To support the preclinical exploration, a scalable synthesis of this molecule was needed. In this communication, a practical, and scalable synthesis of FMCA, and its prodrug are reported *via* ketone **1**. The selective opening of isopropylidene group of **2** led to compound **3**. Protection of the allylic hydroxyl group of **3** followed by fluorination, and deprotection afforded the key intermediate **10**, which was condensed with a Boc-protected adenine followed by deprotection furnished the target nucleoside FMCA (**12)** in high yield. Further coupling of phosphorochloridate of L-alanine isopropyl ester (**13**) with FMCA gave its phosphoramidate prodrug FMCAP (**14)** in good yield.

INTRODUCTION

Hepatitis B virus (HBV) is one of the leading causes of morbidity, and mortality of human population in the world. According to WHO, approximately 2 billion people have been infected with HBV, out of them approximately 350 million people are suffering from chronic HBV infection.[1] Due to the chronic infection of HBV, worldwide 0.5–1.2 million deaths annually are reported. The untreated HBV infection can develop into liver failure, cirrhosis, and eventually hepatocellular carcinoma that will result in an urgent need for liver transplantation. Although various drugs, and vaccines have been introduced for the treatment of the HBV infection, none of them has been successful for its complete eradication.[2] A class of nucleos(t)ides are available for the treatment of chronic HBV infection.[3] These nucleos(t)ides inhibit viral reverse transcriptase (RT)/DNA polymerase which serves as an essential enzyme for the DNA synthesis in HBV. Based on this mechanism, lamivudine was first introduced for the treatment of chronic HBV infection. After a period of therapy, lamivudine-resistant HBV (LVDr) was observed in a significant number of patients.[4] Currently, entecavir and tenofovir alafenamide are the most prescribed drugs for the treatment of HBV.[5] A long-term therapy of these drugs promotes double and triple mutations, and becomes drug-resistant HBV.[6] Recently, the reported triple mutation (L180M+M204V+S202G) limits the use of entecavir/lamivudine.[7] These double and triple mutations of the virus have become a major challenge in the treatment of HBV.[8] Thus, agents effective against drug resistant HBV mutants in patients are critically needed.

For the last two decades, in search of novel antiviral agents, our group has been involved in the discovery of 2′-fluoro containing nucleosides.[9-11] To overcome the current drug resistant

problem of HBV, we discovered 2′-fluoro-6′-methylene carbocyclic adenosine (FMCA) and its phosphoramidate prodrug (FMCAP, Figure 1) as promising anti-HBV agents.[12]

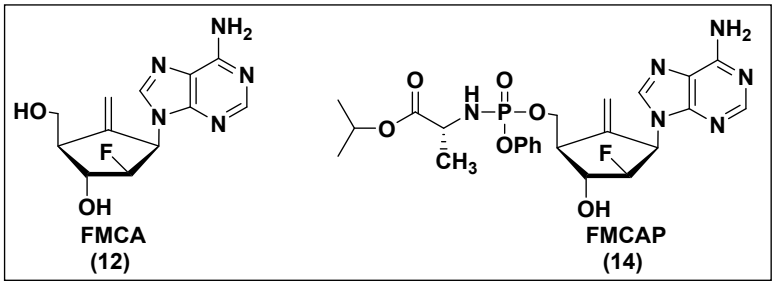


Figure 1. Structures of FMCA and its phosphoramidate prodrug FMCAP.

FMCA has demonstrated a significant activity against the wild-type as well as lamivudine-, adefovir-, and lamivudine/entecavir-resistant mutants.[13] Furthermore, it has also been evaluated against lamivudine/entecavir-resistant clone (L180M+M204V+S202G), that has become a challenge, as it confines the use of currently available drugs for the treatment of HBV. Interestingly, FMCA has shown potential antiviral activity against resistant mutants. It is well known that the first phosphorylation is the rate limiting step for the antiviral activity of the parental nucleoside.[14,15] Thus, to increase the phosphorylation, and thereby the antiviral activity, the prodrug of FMCA was synthesized to bypass the initial phosphorylation step, and it has indeed demonstrated a 12-fold increase in anti-HBV activity against the entecavir/lamivudine-resistant triple mutant (L180M+M204V+S202G).[16] Mitochondrial and cellular toxicity of FMCA, and FMCAP have also been studied, and no significant toxicity was observed up to 100μM.[16] Based on these results it was of great interest to examine further biological evaluation of FMCA to determine its full potential as an anti-HBV agent, which requires a significant amount of FMCA. Consequently, the development of a practical and cost effective synthesis of FMCA/FMCAP was needed.

In our previous communication, we have reported the synthesis of FMCA *via* Vince lactam in 14 steps.[17,18] However, the low yield of certain steps, limits the process for a large scale synthesis. Furthermore, lack of commercial availability of carbocyclic intermediate **1** was also a prime challenge. Our group and others have investigated the synthesis of carbocyclic intermediate **1** from D-ribose, and convenient, but a small scale method has been previously developed.[19] Several commercial vendors adopted this synthesis, and currently the supply of carbocyclic ketone **1** is readily available on demand. Therefore, herein we report a scalable, practical synthesis of FMCA in 7 steps from the carbocyclic ketone **1**. The straightforward reactions as well as the use of readily available reagents make the process feasible for the scalable synthesis of FMCA/FMCAP. During initial optimization of the synthesis, unexpected 2-deoxy carbocylic moieties **6**, and **7** were obtained. It is noteworthy to mention that the generation of 2-deoxy carbocyclic moieties is interesting. The preparation of a 2-deoxy carbocyclic moiety usually requires robust, and expensive synthesis,[20] but generation of **6**, and **7** were critical for this approach as they influence the overall yield. If the process could be optimized to exclusively obtain the 2-deoxy carbocyclic intermediate **6**, this approach might be applied for the synthesis of 2-deoxy cabocyclic nucleosides, which is not the current scope of this report.

RESULTS AND DISCUSSION

Previously, we have reported a stereoselective synthesis of FMCA *via* Vince Lactam.[17] However, poor yields of the diazotization-elimination step of an amino group, as well as the inversion of configuration of the hydroxyl group of the key intermediate makes the synthetic approach challenging for a large scale synthesis of FMCA. In search of a more efficient method for the synthesis of FMCA, herein we report a practical synthesis *via* the intermediate **1**, which is a

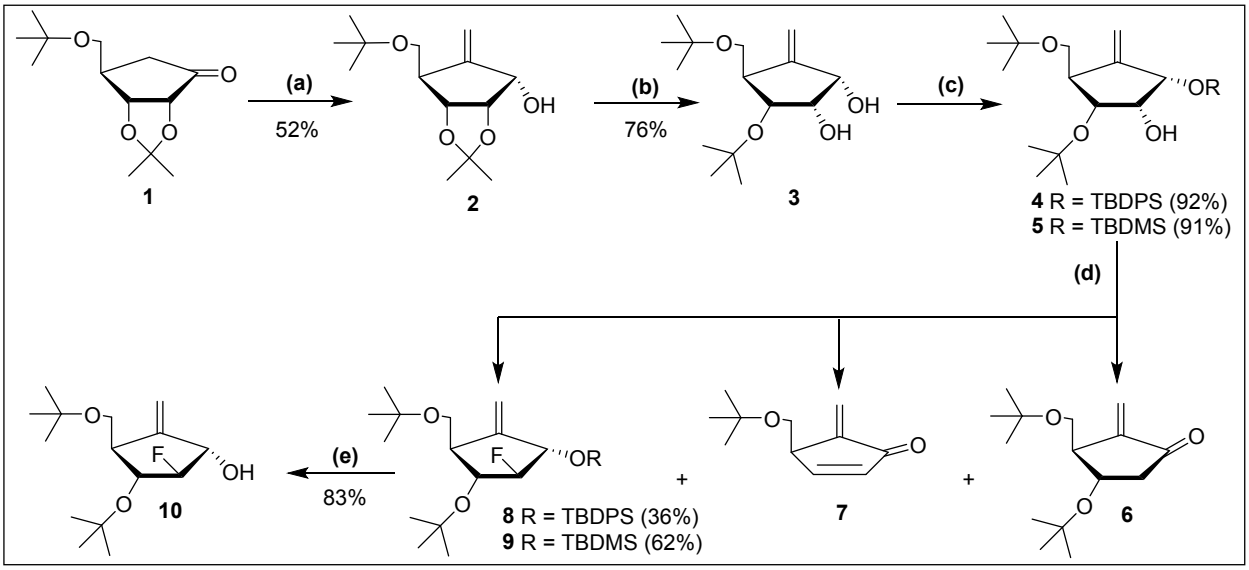
commercially available starting material. The new scheme may provide fewer steps, better overall yield, and also can avoid the column chromatography in several steps.

The synthesis of compound **2** was carried out by the introduction of an exocyclic methylene group to ketone **1**.[16] In our previous report,[21] the incorporation of the exocyclic double bond at 6 position was done by the treatment of ketone **1** with Eschenmoser's salt in the presence of LDA, followed by Hoffman elimination with methyl iodide. The step was very challenging and tedious, and furthermore an excess use of toxic methyl iodide was also not acceptable for a large scale setting. In this report, to avoid these harmful and expensive reagents, the insertion of an exocyclic double bond has been accomplished by the use of paraformaldehyde in the presence of diisopropylamine, and TFA salt.[22]

Thus, the ketone **1** was treated with paraformaldehyde in presence of diisopropyl ammonium trifluoroacetate salt in THF to furnish an enone in 67% yield (scheme 1). Selective reduction of the enone was carried out by using sodium borohydride/cerium chloride hydrate complex ($NaBH_4/CeCl_3.7H_2O$) *via* Luche reduction[23] to obtain exclusively α-hydroxyl compound **2** in 78% yield. A regioselective opening of the isopropylidene group of compound **2** was accomplished by the reported protocol of Ogasawara et al.[24,25] The treatment of compound **2** with trimethylaluminum (2M solution in hexane) produced diol **3** with retention of the α-configuration of hydroxyl groups in 76% yield. Selective protection of allylic alcohol **3** was carried out with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in presence of imidazole in DCM to give the protected compound **4** in 92% yield. Due to the higher reactivity of the allylic alcohol, and bulkier TBDPS group, compound **4** was exclusively obtained.

Conversion of 2-α-hydroxy to 2-β-fluoro intermediate **8** was accomplished by treating the alcohol **4** with diethylaminosulfur trifluoride (DAST) at - 30 ºC to room temperature for 30 minutes to give the 2-fluoro derivative **8** in 36% yield. During the course of the fluorination reaction, an interesting observation was made that is noteworthy to report. The fluorination of compound **4** was carried out by DAST in DCM. To complete the consumption of the starting material **4**, the reaction time was extended from which two additional polar spots appeared along with the desired compound **8** on TLC. These results prompted us to isolate, and identify the two polar spots from the fluorination reaction. The spectral data confirmed the formation of compounds **6**, and **7**. It is noteworthy to mention that the preparation of 2-deoxy intermediates is challenging, and often necessary in nucleoside chemistry. The ketone **6** can be selectively reduced to an alcohol intermediate, which can be utilized for the synthesis of entecavir. [26,27]

Scheme 1. Synthesis of common key intermediate 10



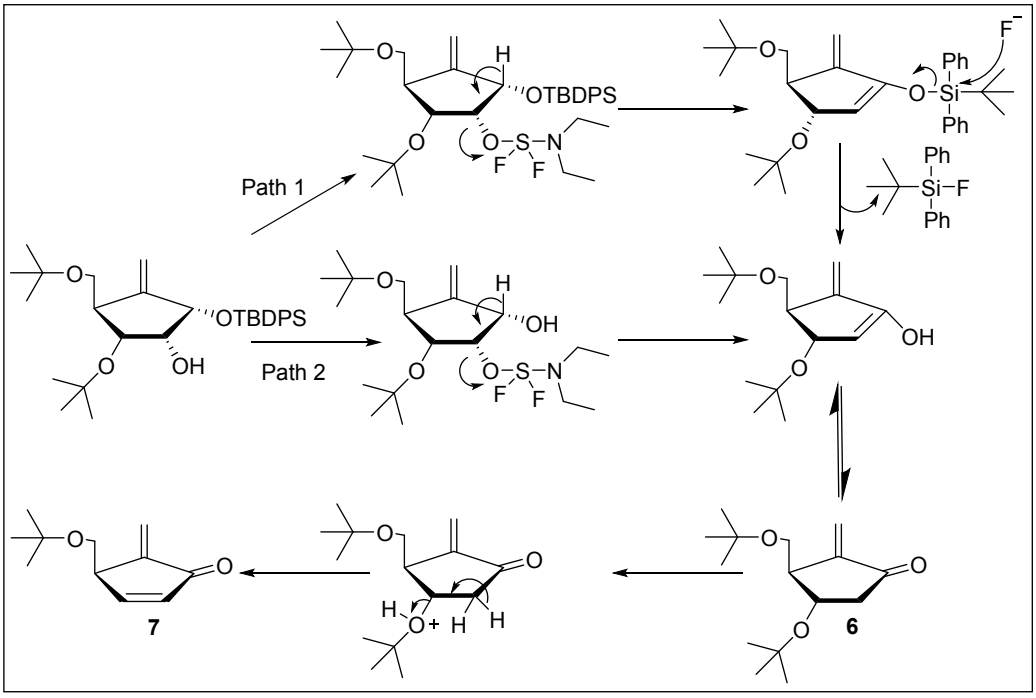
Reagents and Conditions: (a) i) $(HCHO)_n$, *i-Pr*$_2$NH.TFA, diisopropylamine, THF; ii) $NaBH_4$, $CeCl_3.7H_2O$, Methanol; (b) $Al(Me)_3$ (2.0M in hexane), DCM; (c) TBDPSCl or TBDMSCl, imidazole, DCM; (d) DAST, DCM; (e) TBAF, THF.

The structure of compound **6** was validated by ^{1}H NMR, ^{1}H-^{1}H COSY, DEPT-C NMR and HMQC spectroscopy. The ^{1}H NMR spectrum of compound **6** revealed double doublet of two H-2 protons at δ 2.62, 2.26 and a quartet of H-3 proton at δ 4.07 ppm with a complete absence of H-1 proton. ^{1}H-^{1}H COSY spectra of **6** showed the correlation of double doublet of H-2 protons with the quartet of H-3 protons. ^{19}F-NMR of **6** showed a complete absence of a fluorine atom, which confirmed the absence of fluorine atom, and the double doublets of H-2 protons proved the formation of 2-deoxy sugar **6**. For further confirmation, a DEPT experiment was performed which showed three peaks of CH_2 carbon at 118.4, 61.1, 47.5, and two peaks of the CH carbon at 68.1 and 50.4. The HMQC spectra also revealed that double doublet of two H-2 protons at δ 2.62, 2.26 showed correlations with CH_2 carbon at 47.5, which confirmed the structure of the ketone **6**.

Compound **7** was also confirmed by a similar spectral analysis. ^{1}H NMR of compound **7** showed two doublets of H-2, and H-3 protons at δ 7.70, and 6.44 indicated the formation of olefinic protons. The complete absence of 3-O- *tert*-butyl protons was detected by ^{1}H-NMR. Probably, in an acidic medium, the 3-O- *tert*-butyl group was eliminated to give the compound **7**. In the ^{1}H-^{1}H COSY spectrum, the olefinic H-2, and H-3 protons correlation confirmed the adjacent protons to each other. Furthermore, to confirm the structure of compound **7**, DEPT and HMQC experiments were performed. Wherein, in the DEPT experiment two CH_2 were evident at δ 117.7, 64.0, and three CH was obtained at δ 160.9, 135.7 and 45.8 along with single CH_3 at

27.5 ppm. In the HMQC spectrum, carbon at 160.9 showed a correlation with a doublet of H-3 proton at δ 7.70, and carbon at 135.7, which showed the correlation with the doublet of H-2 proton at δ 6.44, providing the evidence of the elimination of 3-O-*tert*-butyl group with formation of conjugated alkene of ketone **7**. A plausible mechanism of formation of compounds **6**, and **7** is shown in scheme 2.

Scheme 2. Plausible mechanism of the formation of compound 6 and 7

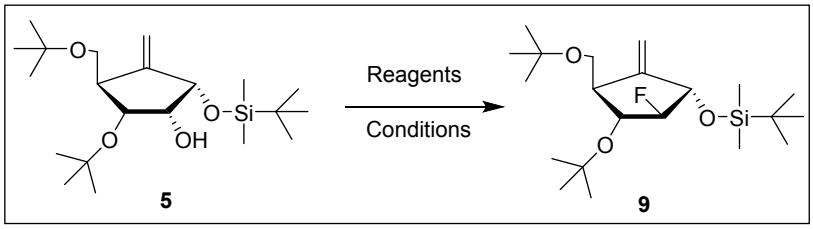


However, due to formation of **6** and **7**, the yield of the fluorination step from **4** to **8** was not acceptable for a large scale synthesis of FMCA. Thus, to improve the yield of fluorination, this reaction was re-examined on compound **5**.

From these observations, it was concluded that the bulky TBDPS group of **4** is playing a major role, and altering the conformation of cyclopentane ring that restricts the favorable fluorine approach to replace the OH group. It is a possibility that the constrained orientation of the carbocyclic ring pushes the elimination of TBDPS to generate **6** & **7** along with the desired

compound **8**. For our purpose, these results were not encouraging. Consequently, another strategy was to change the C1-protecting group of **4**, and then optimize the fluorination reaction to increase the yield of desired fluorinated compound **8**. However, the selective protection of the 1-allylic OH of **3** was also challenging, as the different selective protecting groups were tried, but in each case the di-hydroxy protected compound was obtained as the major product. Hicks et al. reported[28] the selective hydroxy allylic protection with triethylsilane chloride (TESCl), but our result were not encouraging, and with the ratio of 6/4 in favor of the desired-mono/undesired-di-protected compound were obtained. Alternatively, the treatment of compound **3** with *tert*-butyldimethylsilyl chloride yielded selectively allylic protected compound **5** in 91% yield. Furthermore, the fluorination of compound **5** with DAST furnished the compound **9** in 62% yield with traces of compounds **6**, and **7**. To further improve the yield of the fluorination, a variety of fluorinating reagents *via* S_N2 type fluorination were also tried with various reactions conditions, but none of them gave any improved yield of the compound **9**. The results are summarized in Table 1.

Table 1. The optimization of fluorination of compound 5 with various fluorinating agents.



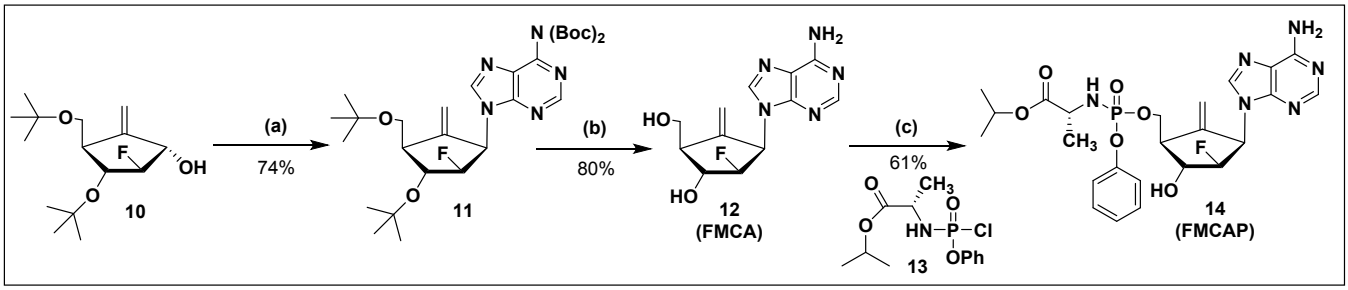
5 **9**

Entry	Reagent	Additive (equiv)	Solvent	T (°C)	Time	Yield (%)
1.	DAST	1.5	DCM	-20 °C to r.t.	0.5 h	38%
2.	DAST	3	DCM	-20 °C to r.t.	0.5 h	48%
3.	DAST	7	DCM	-20 °C to r.t.	10 min	62%

4.	Xtal Fluor-E, DBU[29]	1 : 1.5	DCM	-78 °C to r.t.	4.0 h	10% Deprotection of TBDMS was observed
5.	Xtal Fluor-E, TEA.3HF, TEA[29]	1.5 : 2 : 1	DCM	-78 °C to r.t.	20 min	35%
6.	Xtal Fluor-E, TEA.3HF, TEA	3 : 4 : 2	DCM	-78 °C to r.t.	30 min	30%
7.	Xtal Fluor-E, TEA.3HF, TEA	1.5 : 2.0 : 1	Toluene	-78 °C to r.t.	1 h	25%
8.	Xtal Fluor-M, TEA.3HF, TEA[29]	1.5 : 2.0 : 1	DCM	-78 °C to r.t.	1 h	25%
9.	Fluolead[30]	2	DCM	0 °C to r.t.	30 min	42%
10.	Fluolead	4	DCM	0 °C to r.t.	30 min	25%
11.	PyFlour, DMAP[31]	1 : 1.5	Toluene	0 °C to r.t.	24 h	starting material was as such
12.	PyFlour, DMAP	1 : 1.5	Toluene	80 °C	4 h	starting material was as such
13.	Ishikawa's Reagent (N,N-diethyl-1,1,2,3,3,3-hexafluoropropylamine)	3	DCM	0 °C to r.t.	3 h	undesired spots were formed (not isolated)
14.	Yarovenko reagent (2-chloro-1,1,2-trifluoroethyl-N,N-diethylamine)	3	DCM	0 °C to r.t.	6 h	undesired spots were formed (not isolated)

Note: The entry 3 was found the most suitable reaction condition for the fluorination of compound **5**.

Scheme 3. Synthesis of FMCA and FMCAP from common intermediate 10



Reagents and Conditions: (a) *N, N*-diBoc-adenine, DIAD, TPP, THF; (b) TFA, DCM; (c) Compound **13**, NMI, THF.

TBDMS deprotection of compound **9** was accomplished by tetrabutylammonium fluoride (TBAF). Compound **9** was treated with a 2M solution of TBAF in THF at room temperature to give the key intermediate compound **10** in 83% yield. The compound **10** was condensed with *N,*

N-diBoc protected adenine under Mitsunobu coupling conditions using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (TPP) in THF to give **11** in 74% yield (scheme 3). The *tert*-butyl, and Boc protecting groups of compound **11** were removed by using 2M trifluoroacetic acid (TFA) in DCM at room temperature, affording the nucleoside **12** (FMCA) in 80% yield. The phosphoramidate prodrug (FMCAP) was synthesized by condensing FMCA with compound **13**. Compound **13** was furnished by treating phenyl dichlorophosphate with L-alanine isopropyl ester in DCM at -78 ºC. Finally, FMCA was treated with **13** in the presence of *N*-methyl imidazole (NMI) in THF at room temperature to obtain the target compound **14** in 61% yield.

CONCLUSION

To determine the full biological evaluation of FMCA and FMCAP, an efficient and scalable synthetic method of FMCA has been developed *via* commercially available ketone **1**. The selective opening of acetonide of compound **2** followed by the allylic protection of **3** gave compound **5**. Fluorination of compound **5**, and subsequent deprotection of TBDMS yielded the key intermediate **10**. Mitsunobu coupling with Boc-protected adenine followed by the deprotection afforded the target compound **12** (FMCA) in 7 steps with approximately 8.9 % overall yield *via* TBDMS protected compound **5**. This process may serve as more efficient than the previously reported method for scalable synthesis of FMCA. Further coupling of phosphorochloridate **13** with FMCA produced phosphoramidate prodrug **14 (**FMCAP). The reduction of synthetic steps in comparison to the previous method, and the use of economical reagents make this methodology amenable for a large scale preparation of FMCA.

EXPERIMENTAL SECTION

General Analytical Methods

Reagents and anhydrous solvents were purchased, and used without further purification. Reactions were monitored by thin-layer chromatography plates (TLC silica gel GF 250 microns) that were visualized using a UV lamp (254 nm), and developed with 15% solution of sulfuric acid in methanol. Melting points were recorded on a digital melting point apparatus, and are uncorrected. Nuclear magnetic spectra were recorded on 500 MHz for ^{1}H NMR, 470 MHz for ^{19}F NMR and 125 MHz for ^{13}C NMR with tetramethylsilane as an internal standard. $CFCl_3$ (trichloro-fluoro methane was used as the internal standard **(**reference) for ^{19}F NMR. Chemical shifts (δ) are quoted as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (double doublet) and dt (double triplet). Optical rotations were measured on a digital polarimeter. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Thin layer chromatography was performed on a glass plate coated with silica gel.

(*3aS*,*4S*,*6R*,*6aR*)-6-(*tert*-Butoxymethyl)-2,2-dimethyl-5-methylenetetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (2). To a stirred suspension of **1** (50.0 g, 206.6 mmol), and paraformaldehyde (12.4 g, 413.2 mmol) in dry THF, diisopropyl ammonium trifluoroacetate (44.4 g, 206.6 mmol), and diisopropylamine (29.0 mL, 206.6 mmol) were added. The suspension was refluxed for 2 h. After that the mixture was cooled to room temperature, and additional portion of paraformaldehyde (12.4 g, 413.2 mmol) was added. The reaction mixture was again refluxed for 12 h. The mixture was concentrated under reduced pressure, and residue was diluted with 1 L of ethyl acetate. The organic layer was washed with water (400 mL X 3), and dried over Na_2SO_4, and concentrated in vacuo to afford the crude product that was used as such for the next step. The crude material (52.0 g, 200.7 mmol) was dissolved in anhydrous methanol (500 mL),

$CeCl_3.7H_2O$ (98.7 g, 265.0 mmol) was added at -78 ºC, and stirred for 20 minutes. Then $NaBH_4$ (9.7 g, 256.9 mmol) was added portion wise to the mixture. After 20 minutes stirring at the same temperature, the reaction mixture was warmed to 0 ºC, and stirred for 30 minutes. A saturated solution of NH_4Cl (200 mL) was added, and stirred for additional 1 h. Excess organic solvent was removed under reduced pressure, and 10% aqueous acetic acid solution (100 mL) was added. The aqueous layer was extracted with ethyl acetate (200 mL X 2); combined organic extracts were washed with brine (200 mL X 2), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOAc/hexane) to give compound **2** as a white solid. (Yield 27 g, 52 % overall yield in 2 steps). Mp 58-60 °C; $[\alpha]^{24}_D$ = -118.2° (c 0.42, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 (s, 1H), 5.11 (s, 1H), 4.50-4.53 (m, 3H), 3.46 (dd, *J* = 3.5 & 8.5 Hz, 1H), 3.27 (dd, *J* = 3.5 & 8.5 Hz, 1H), 2.63 (t, *J* = 3.5 Hz, 1H), 2.25 (d, *J* = 11.0 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.12 (s, 9H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.9, 110.2, 109.3, 81.6, 79.3, 73.8, 72.7, 64.3, 49.9, 27.3, 26.5, 24.7; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{24}O_4Na$ 279.1572; Found 279.1577.

(*1S,2R,3S,4R*)-3-(*tert*-Butoxy)-4-(*tert*-butoxymethyl)-5-methylenecyclopentane-1,2-diol (3). Compound **2** (40.0 g, 156.2 mmol) was dissolved in 500 mL of DCM, and cooled to -78 ºC. Trimethylaluminum solution (2M solution in hexane, 986.0 mL, 1562.5 mmol) was added, and mixture was stirred at ambient temperature for 72 h. The mixture was cooled to -78 ºC, and saturated ammonium chloride solution (200 mL) was added dropwise. The mixture was passed through a celite bed, and was thoroughly washed with dichloromethane (250 mL X 2). Filtrate was dried over Na_2SO_4, concentrated under reduced pressures. The crude was purified by silica gel column chromatography (10% EtOAc/hexane) gave compound **3** as off-white solid. Yield (32.4 g, 76 %). Mp 62-65 °C; $[\alpha]^{24}_D$ = -70.24 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34

(s, 1H), 5.13 (s, 1H), 4.26 (d, *J* = 10.0 Hz, 1H), 4.09 (s, 1H), 3.95-3.92 (m, 1H), 3.46 (dd, *J* = 4.0 & 8.5 Hz, 1H), 3.37 (dd, *J* = 5.0 & 8.0 Hz, 1H), 2.88 (d, *J* = 2.0 Hz, 1H), 2.65 (bs, 1H), 2.50 (d, *J* = 11.0 Hz, 1H), 1.27 (s, 9H), 1.17 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 152.4, 150.0, 109.9 (d, *J* = 6.0 Hz), 75.8, 74.9, 72.4, 62.2, 48.8, 28.5, 27.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{28}O_4Na$ 295.1885; Found 295.1882.

(*1S,2S,3R,5S*)-2-(*tert*-Butoxy)-3-(*tert*-butoxymethyl)-5-((*tert*-butyldiphenylsilyl)oxy)-4-methylenecyclopentan-1-ol (4). Compound **3** (20.0 g, 73.5 mmol), and imidazole (20.0 g, 294.1 mmol) were dissolved in anhydrous DCM (250 mL) at 0 ºC, and mixture was stirred for 15 minutes. *tert*-Butyldiphenylsilyl chloride (28.7 mL, 110.2 mmol) was added, and stirring was continued for 4 h at room temperature. To the mixture 300 mL of water was added, and separated organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3% EtOAc/Hexane) to give **4** as oil. Yield: (34.6 g, 92%). $[\alpha]^{24}_D$ = -16.42 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.35-7.28 (m, 6H), 5.11 (s, 1H), 4.93 (s, 1H), 4.28 (s, 1H), 3.73 (s 1H), 3.49 (s, 1H), 3.28-3.26 (m, 2H), 2.63 (s, 1H), 2.49 (bs, 1H), 1.06 (s, 9H), 1.04 (s, 9H), 0.96 (s, 9H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 151.6, 135.8 (d *J* = 12.8 Hz), 135.8, 135.3, 134.8, 134.1, 133.6, 129.6, 127.7 (d, *J* = 20.0 Hz), 74.1, 72.0, 61.8, 28.4, 27.4, 26.9, 26.6, 19.4, 19.0, 14.1; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{46}O_4SiNa$ 533.3063; Found 533.3059.

(*1S,2S,3R,5S*)-2-(*tert*-Butoxy)-3-(*tert*-butoxymethyl)-5-((*tert*-butyldimethylsilyl)oxy)-4-methylenecyclopentan-1-ol (5). Compound **3** (15.0 g, 55.1 mmol), and imidazole (15.0 g, 220.4 mmol) were dissolved in anhydrous DCM (300 mL), and the mixture was stirred for 15 minutes at 0 ºC. *tert*-Butyldimethylsilyl chloride (13.2 g, 88.2 mmol) was added, and stirring was

continued for 3 h at room temperature. The reaction mixture was diluted with water (300 mL), and separated organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The crude was purified by silica gel column chromatography (4% EtOAc/Hexane) to give **5** as oil. Yield: (19.5 g, 91 %). $[\alpha]^{24}_D$ = -59.42 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (d, *J* = 2.0 Hz, 1H), 4.88 (s, 1H), 4.20 (t, *J* = 3.5 & 1.0 Hz, 1H), 3.87 (t, *J* = 7.5 & 3.5 Hz, 1H), 3.71 (s, 1H), 3.33-3.30 (m, 2H), 2.53 (s, 1H, OH), 2.46 (bs, 1H), 1.16 (s, 9H), 1.01 (s, 9H), 0.82 (s, 9H), 0.01 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 156.6, 112.2, 78.9 (d, *J* = 18.6 Hz), 76.9, 76.0 (d, *J* = 20.0 Hz), 66.3, 52.6 (d, *J* = 20 Hz), 33.4 (d, *J* = 18.1 Hz), 32.4 (d, *J* = 14.7 Hz), 30.7 (d, *J* = 12.5 Hz), 23.2, 0.13; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{43}O_4Si$ 387.2931; Found 387.2929.

(((*1S,2R,3S,4R*)-3-(*tert*-Butoxy)-4-(*tert*-butoxymethyl)-2-fluoro-5-methylenecyclopentyl) oxy)(*tert*-butyl)diphenylsilane (8). To a solution of compound **4** (20.0 g, 39.2 mmol) in anhydrous DCM (250 mL), DAST (36.4 mL, 274.4 mmol) was added dropwise at -30 °C. The mixture was warmed to room temperature, and stirred for 30 min. The mixture was cooled to -30 °C, and quenched with ice cold water. The aqueous layer was extracted with DCM (200 mL X 2). The combined organic extracts were washed with brine (100 mL X 2), and finally with water (100 mL), dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1% EtOAc/hexane) to give **8** as yellowish oil. Yield (7.2 g, 36 %). $[\alpha]^{24}_D$ = -30.17 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75-7.73 (m, 4H), 7.46-7.38 (m, 6H), 5.12 (s, 1H), 4.94 (s, 1H), 4.68 (dt, *J* = 50.0 & 75.0 Hz, 1H), 4.64-4.60 (m, 1H), 4.04-3.99 (m, 1H), 3.42 (dd, *J* = 4.0 & 8.0 Hz, 1H), 3.32 (dd, *J* = 4.0 & 8.5 Hz, 1H), 2.50 (bs, 1H), 1.22 (s, 9H), 1.15 (s, 9H), 1.06 (s, 9H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -188.8 (dt, *J* = 16.5 & 53.1 Hz, 1F); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 148.1 (d, *J* = 9.5 Hz), 135.9 (d, *J* = 10.0

Hz), 134.1, 133.6, 129.5 (d, J = 10. 0 Hz), 127.4, 109.1, 104.1, 73.9, 72.2, 61.9, 48.3, 31.6, 28.8, 27.3, 27.0, 22.6, 19.5; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{31}H_{45}FO_3SiNa$ 535.3020; Found 535.3017. The two polar compounds **6**, and **7** formed in this reaction, were purified, with an elevated polarity of eluent to 10-20%, EtOAc/hexane gave the purified compound **6** (2.39g, 24%), and **7** (1.41g, 20%) as an oil.

(*3R, 4R)*-4-(*tert*-Butoxy)-3-(*tert*-butoxymethyl)-2-methylenecyclopentan-1-one (6). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.33 (s, 1H), 4.07 (q, J = 6.0 &12.0 Hz, 1H), 3.45 (m, 2H), 2.76 (bs, 1H), 2.62 (dd, J = 7.0 &18.5 Hz, 1H), 2.26 (dd, J = 6.0 & 18.0 Hz, 1H), 1.13 (s, 9H), 1.10 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 205.1, 1.45.4, 118.4, 74.2, 72.8, 68.3, 61.1, 50.4, 47.5, 28.6 (d, J = 15.2 Hz), 27.5; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{27}O_3$ 255.1960; Found 255.1956.

(*R*)-4-(*tert*-Butoxymethyl)-5-methylenecyclopent-2-en-1-one (7). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 6.0 Hz, 1H), 6.44 (d, J = 5.5 Hz, 1H), 6.15 (s, 1H), 5.59 (s, 1H), 3.56 (bs, 2H), 3.37 (bs, 1H), 1.22 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 196.8, 160.0, 143.6, 135.9, 117.8, 73.5, 64.1, 45.9, 27.7; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{17}O_2$ 181.1229; Found 181.1224.

(((*1S,2R,3S,4R*)-3-(*tert*-Butoxy)-4-(*tert*-butoxymethyl)-2-fluoro-5-methylenecyclopentyl) oxy)(*tert*-butyl)dimethylsilane (9). To a solution of compound **5** (15.0 g, 38.8 mmol) in anhydrous DCM (200 mL), DAST (35.8 mL, 272.0 mmol) was added dropwise at -30 °C. The mixture was warmed to room temperature with stirring for 10 min. The mixture was cooled to -30 °C, and quenched with ice cold water. The aqueous layer was extracted with DCM (200 mL X 2). The combined organic extracts were dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1.5% EtOAc/hexane)

to give **9** as oil. Yield (9.3 g, 62.0 %). $[\alpha]^{24}_{D}$ = -68.32 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.84 (s, 1H), 4.39 (d, *J* = 4.5 Hz, 1H), 4.32 (dt, *J* = 8.0 & 45.0 Hz, 1H), 3.97 (dt, *J* = 6.0 & 17.0 Hz, 1H), 3.37 (dd, *J* = 4.0 & 9.0 Hz, 1H), 3.29-3.26 (m, 1H), 2.34 (bs, 1H), 1.10 (s, 9H), 1.04 (s, 9H), 0.82 (s, 9H), 0.00 (s, 6H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -190.5 (dt, *J* = 16.5 & 52.6 Hz, 1F); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.4 (d, *J* = 10.5 Hz), 112.8, 108.3 (d, *J* = 191.0 Hz), 81.6 (m), 78.5, 67.0 (t, *J* = 8.6 & 18.1 Hz), 53.1 (d, *J* = 22.9 Hz), 33.8 (d, *J* = 15.8 Hz), 32.5 (d, *J* = 14.4 Hz), 30.8 (dd, *J* = 10.5 & 31.4 Hz), 23.3, 0.27, 0.26, 0.17, 0.08; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{41}FO_3SiNa$ 411.2707; Found 411.2702.

(*1S,2S,3S,4R*)-3-(*tert*-Butoxy)-4-(*tert*-butoxymethyl)-2-fluoro-5-methylenecyclopentan-1-ol (10). To a solution of compound **9** (9.2 g, 23.7 mmol) in THF (150 mL), tetrabutylammonium fluoride (TBAF, 1M solution in THF) (35.5 mL, 35.5 mmol) was added, and the mixture was stirred at room temperature for 3 h. The solvent was removed under reduced pressure, and obtained residue was dissolved in ethyl acetate (250 mL). The organic layer was washed with water (200 mL X 2), and finally with brine solution (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography (4% EtOAc/hexane) to afford compound **10** as white foam. Yield (5.4 g, 83%). $[\alpha]^{24}_{D}$ = -76.69 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (s, 1H, 7-H), 5.15 (s, 1H, 7-H), 4.55 (dt, *J* = 5.5 & 53.5 Hz, 1H, 2-H), 4.53-4.51 (m, 1H, 1-H), 4.19-4.16 (m, 1H, 3-H), 3.49-3.47 (m, 1H, 5-H), 3.42-3.40 (m, 1H, 5-H), 2.64 (bs, 1H, 4-H), 2.28 (d, *J* = 8.0 Hz, 1H, 1-OH), 1.26 (s, 9H, 3-OC$(CH_3)_3$), 1.19 (s, 9H, 5-OC$(CH_3)_3$); ^{19}F NMR (470 MHz, $CDCl_3$) δ -190.6 (dt *J* = 13.1 & 53.1 Hz, 1F); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.0, 149.0 (d, *J* = 6.6 Hz), 102.2 (d, *J* =189.2 Hz), 74.7, 72.6, 62.0, 48.9, 28.6, 27.4; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{15}H_{27}FO_3Na$ 297.1842; Found 297.1839.

9-((*1R,3R,4R*)-3′-*tert*-Butoxy-4′-(*tert*-butoxymethyl)-2′-fluoro-5′-methylenecyclopentyl)-*N,N*-diboc-9H-purin-6-amine (11). To a stirred solution of triphenylphosphine (4.78 g, 18.24 mmol), in THF (50 mL) at -10 °C, was added DIAD (3.68 g, 18.24 mmol) dropwise, and mixture was stirred at this temperature for 30 minutes. *N, N*-diBoc-protected adenine (3.7 g, 10.9 mmol) solution in THF (20 mL) was added, and the mixture was stirred for 30 min at 0 °C. Compound **10** (2.0 g, 7.29 mmol) in THF (10 mL) was then added dropwise, and the reaction mixture was stirred at room temperature for 1.5 h. The reaction mixture was quenched with methanol, and solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (5% EtOAc/ hexane) to give **11** as white foam. Yield (3.2 g, 74%). $[\alpha]^{24}_{D}$ = -51.47 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (s, 1H, 8-H), 8.24 (s, 1H, 2-H), 5.97 (d, *J* = 30.5 Hz, 1H, 1′-H), 5.32 (s, 1H, 7′-H), 4.90 (dd, *J* = 9.0 & 52.5 Hz, 1H, 2′-H), 4.77 (s, 1H, 7′-H), 4.33 (d, *J* = 14.0 Hz, 1H, 3′-H), 3.62-3.60 (m, 1H, 5′-H), 3.54-3.50 (m, 1H, 5′-H), 2.85 (bs, 1H, 4′-H), 1.47 (s, 18H, 6-N$(Boc)_2$), 1.28 (s, 9H, 3′-OC$(CH_3)_3$), 1.27 (s, 9H, 5′-OC$(CH_3)_3$); ^{19}F NMR (470 MHz, $CDCl_3$) δ -191.1 (ddd, *J* = 14.1, 32.9 & 46.0 Hz, 1F); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 153.9, 152.0, 150.3 (d, *J* = 20.0 Hz), 150.0, 146.4, 145.3, 128.1, 110.8 (d, *J* = 219.8 Hz), 83.7, 75.7, 73.2, 62.6, 49.8, 28.2, 27.8, 27.5; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{30}H_{47}FN_5O_6$ 592.3510; Found 592.3509.

(+)-9-[(1′*R*, 2′*R*, 3′*R*, 4′*R*)-2′-Fluoro-3′-hydroxy-4′-(hydroxymethyl)-5′-methylene-cyclopentan-1′-yl]adenine (FMCA, 12). To a solution of compound **11** (3.3 g, 5.58 mmol) in DCM (30 mL), trifluoroacetic acid (6 mL) was added, and the mixture was stirred at ambient temperature for 16 h. The excess solvent was removed under reduced pressure, and residual TFA was co-evaporated three times with methanol. The residue was diluted with methanol, and neutralized with 28% aqueous ammonia solution, concentrated under reduced pressure. The

crude was purified by column chromatography on silica gel (6% Methanol/DCM) to give **12** as white solid. Yield (1.2 g, 80%). Mp 215-218 °C; $[\alpha]^{24}_{D}$ = +152.10° (c 0.5, MeOH); UV (H_2O) λ_{max} 259.0 nm (ε 14000, pH 2), 260.0 nm (ε 15600, pH 7), 260.0 nm (ε 15600, pH 11); ^{1}H NMR (500 MHz, CD_3OD) δ 8.26 (s, 1H, 8-H), 8.10 (d, *J* = 2.5 Hz, 1H, 2-H), 5.90 (d, *J* = 26.0 Hz, 1H, 1′-H), 5.46 (s, 1H, 7′-H), 4.96 (dt, *J* = 2.5 & 52.5 Hz, 1H, 2′-H), 4.95 (s, 1H, 7′-H), 4.44 (dd, *J* = 6.0 & 14.0 Hz, 1H, 3′-H), 3.88-3.82 (m, 2H, 5′-H), 2.81 (bs, 1H, 4′-H); ^{19}F NMR (470 MHz, CD_3OD) δ -195.95 (ddd, *J* = 13.2, 26.3 & 39.5 Hz, 1F); ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 156.0, 152.5, 149.9, 146.0, 141.1, (d, *J* = 5.3 Hz), 117.9, 111.7, 95.9 (d, *J* = 184.0 Hz), 72.9 (d, *J* = 23.6 Hz), 61.7, 57.5 (d, *J* = 17.4 Hz), 51.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{15}FN_5O_2$ 280.1210; Found 280.1216.

{[(*1R*,*3R*,*4R*)-3-(6-Amino-9H-purin-9-yl)-4-fluoro-5-hydroxy-2-methylenecyclopentyl) methoxy](phenoxyphosphoryl amino} propionic Acid Isopropyl Ester (14). To a solution of phenyl dichlorophosphate (1.0 mol equiv), and the L-alanine isopropyl ester hydrochloride (1.0 mol) in anhydrous DCM at -78 ºC, triethylamine (2.0 mol) was added dropwise, and mixture was stirred at same temperature for 1 h. The reaction mixture was slowly warmed to room temperature, and stirred for 2 h. The solvent was removed under reduced pressure, and crude residue was re-suspended in anhydrous ether, and filtered through a celite bed under nitrogen. The filtrate was concentrated in vacuo to give compound **13**, which was used as such for next step.

To a stirring suspension of compound **12** (0.5 g, 1.79 mmol) in anhydrous THF, *N*-methylimidazole, NMI (0.9 mL, 10.7 mmol) was added at 0 ºC. The phosphorochloridate **13** (2.2 g, 7.1 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred for 12 h at ambient temperature. The volatiles were removed under reduced pressure, and the residue was

purified by silica gel column chromatography (2% Methanol/DCM) to give the compound **14** as off-white solid. Yield (0.55 g, 61%). Mp 56-60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ d 8.29 (s, 1H), 7.84 (d, J = 24.5 Hz, 1H), 7.28-7.10 (m, 5H), 5.88 (d, J = 30.0 Hz, 1H), 5.80 (bs, 2H), 5.18 (d, J = 9.0 Hz, 1H), 4.96-4.76 (m, 3H), 4.39-4.34 (m, 2H), 4.17- 4.04 (m, 2H), 3.90-3.88 (m, 2H), 3.00 (bs, 1H), 1.31 (d, J = 6.5 Hz, 3H), 1.16 (dd, J = 6.0, & 14.0 Hz, 6H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -192.9-193.0 (m, 1F); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 2.84, 2.37; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.3, 155.4, 153.1, 150.5, 144.5, 140.9, 129.8, 125.2, 120.2, 118.7 112.3, 95.6 (J = 169.2 Hz), 73.8 (d, J = 15.0 Hz), 69.5, 66.9, 57.1, 50.2 (d, J = 103.0 Hz), 21.6, 21.0; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{31}FN_6O_6P$ 549.2027; Found 549.2026.

ASSOCIATED CONTENT

Supporting Information: Copies of ^{1}H NMR, ^{19} F NMR and ^{13}C NMR spectra of compounds **3-14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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