



Cite this: DOI: 10.1039/c5ob01348h

Regio- and stereoselective synthesis of 2'- β -substituted-fluoroneplanocin A analogues as potential anticancer agents†

Akshata Nayak,^{a,b} Pramod K. Sahu,^a Jayoung Song,^a Sang Kook Lee^a and Lak Shin Jeong^{*a}

A series of 2'- β -substituted-6'-fluoro-cyclopentenyl-pyrimidines and -purines **8** and **9** were successfully synthesized from D-ribose in a regio- and stereoselective manner. The functionalization at the C2-position of 6'-fluoro-cyclopentenyl nucleosides was achieved *via* regioselective protection of a hydroxyl group at the C3-position and stereoselective formation of C2-triflate followed by direct S_N2 reaction with a fluoro or azido nucleophile. All the synthesized compounds were evaluated for their anticancer activities in several tumor cell lines, but were found to be neither active nor toxic.

Received 3rd July 2015,
Accepted 21st July 2015

DOI: 10.1039/c5ob01348h

www.rsc.org/obc

Introduction

Modified nucleosides which are good substrates for cellular kinases, but resistant to other host enzymes such as phosphorylases which cleave the glycosidic bond of natural nucleosides, are in need for the development of useful therapeutic agents. One of the ways has been isosteric replacement of the furanose oxygen of ribose moieties with methylene groups which are referred as carbocyclic nucleosides.^{1–3} This modification resulted in the substantial metabolic stability towards phosphorylases and hydrolases eliminating the labile glycosidic bond. Interestingly, these carbanucleosides are also recognized by the same enzymes that recognize normal nucleosides. A number of carbocyclic nucleosides are endowed with potent biological activities, especially antiviral and anticancer properties (Fig. 1).^{4,5}

A naturally occurring neplanocin A (**1**)^{6,7} is a representative carbanucleoside, exhibiting potent antiviral and antitumor activities. Its mechanism of action^{8–11} has been well explored and elucidated; phosphorylation at the 5'-position by adenosine kinase and subsequent metabolism by a cellular enzyme leads to anticancer effect, while the broad-spectrum antiviral activity is correlated with the potent inhibitory effect against S-adenosylhomocysteine (SAH) hydrolase.¹² The corresponding cytosine analogue **2**¹³ was also synthesized and reported to exhibit potent anticancer activity. It is phosphorylated intra-

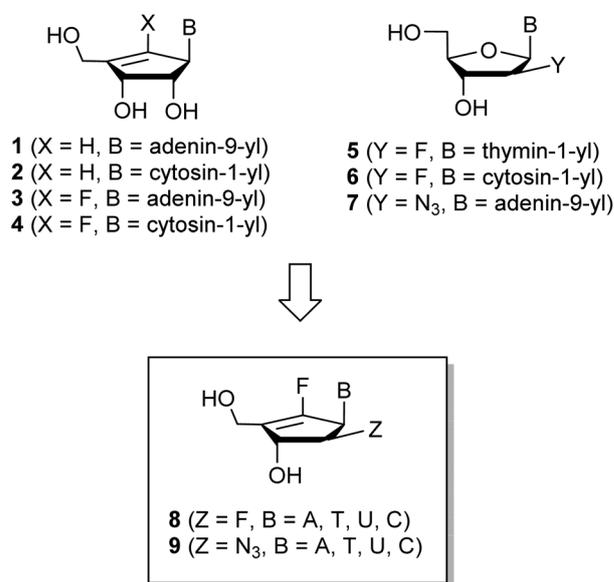


Fig. 1 The rationale for the design of target nucleosides.

cellularly to its triphosphate which then acts as a potent inhibitor of CTP synthetase and thus produces a profound depletion of CTP as well as CDP, dCDP, and dCTP pools.¹³ On the basis of the structures of **1** and **2**, the corresponding 6'-fluoro analogues **3**¹⁴ and **4**¹⁵ were synthesized. Compound **3** was reported to be a dual acting inhibitor of SAH hydrolase along with excellent antiviral activity against the vesicular stomatitis virus (VSV) (EC₅₀ = 0.43 μ M),¹⁴ while compound **4** was reported to show a different mode of action¹⁶ from **2**. It was found that after being activated by uridine-cytidine kinase

^aResearch Institute of Pharmaceutical Sciences, College of Pharmacy, Seoul National University, Seoul 151-742, Korea. E-mail: lakjeong@snu.ac.kr; Tel: +82-2-880-7850

^bCollege of Pharmacy, Ewha Womans University, Seoul 120-750, Korea

†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ob01348h

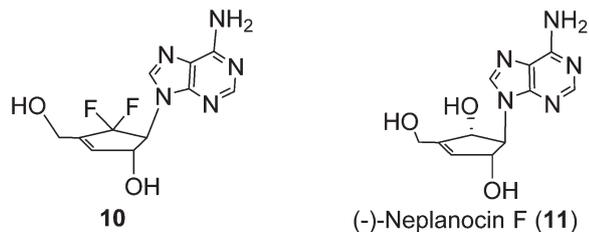


Fig. 2 The structure of bioisosteric compound **10** of (-)-neplanocin F (**11**).

(UCK), **4** is triphosphorylated and incorporated into DNA and RNA¹⁶ and/or inhibits DNA methyltransferase (DNMT).¹⁵

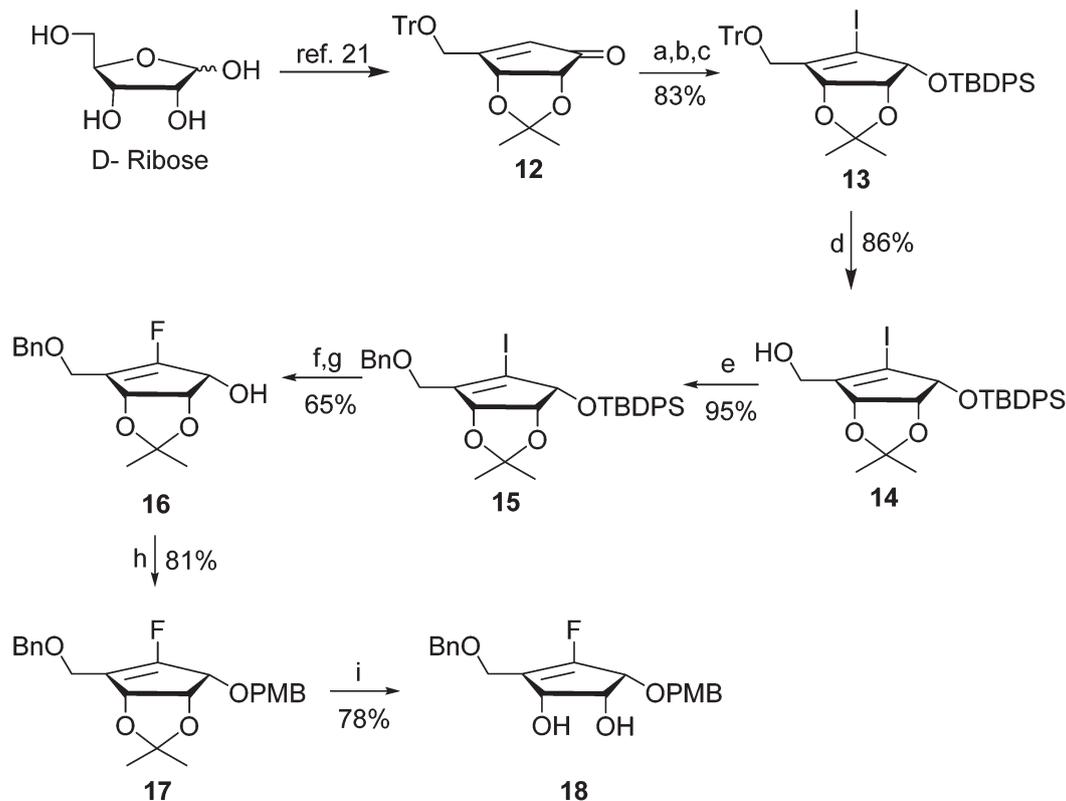
On the other hand, hydrogen or hydroxyl at the C2-position of furanose moiety plays a unique role in differentiating DNA and RNA. Thus, natural and modified nucleosides containing substituents other than hydrogen or hydroxyl groups at this position further encouraged the investigation of the biological properties of nucleosides.¹⁷ As a result substitution at the 2'-position of ribose moiety with fluorine afforded new nucleoside analogues such as FMAU (**5**) or F-ara-C (**6**) with potent antiviral and anticancer properties, respectively (Fig. 1).^{17,18} In addition 2'- β -azido derivative **7**¹⁹ was also reported to display considerable biological activities.

Therefore, based on these findings, it was interesting to design and synthesize the 2'- β -substituted-6'-fluorocyclopent-ynyl-pyrimidines and -purines **8** and **9** which hybridized the structures of 6'-fluorocarbanucleosides **1–4** and 2'- β -substituted nucleosides **5–7** and to evaluate their inhibitory activity against several tumor cell lines. In addition, the unusual *gem*-difluoro intermediate obtained during the synthesis of the target nucleosides was also converted to another final nucleoside **10** (Fig. 2), which may serve as the bioisostere of (-)-neplanocin F (**11**).²⁰

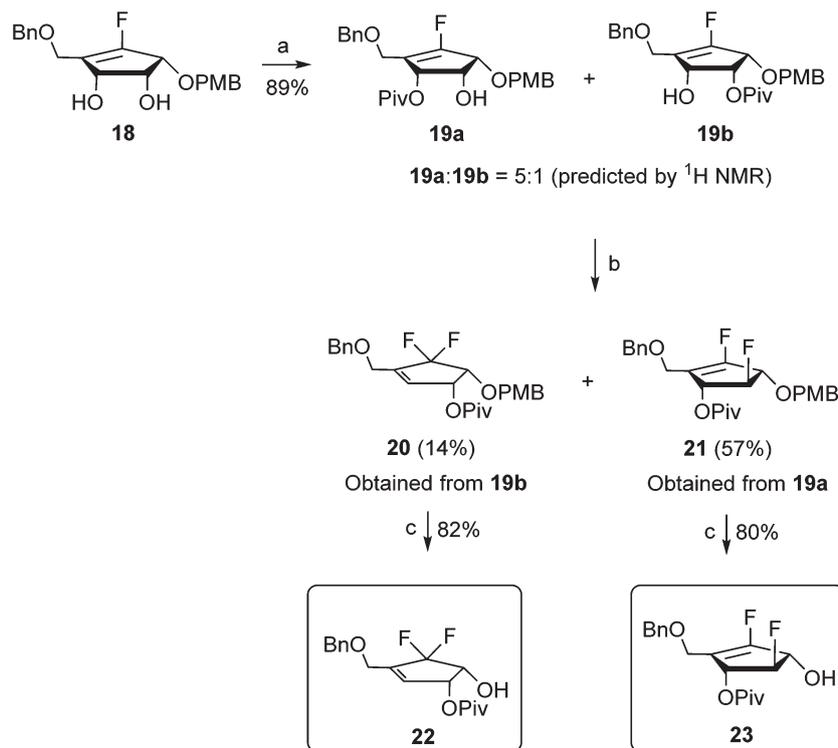
Results and discussion

For the functionalization at the C2 position with fluoride or azide, we decided to utilize the regioselective protection of the allylic hydroxyl group of diol **18** with bulky protecting groups such as trityl (Tr), *tert*-butyldiphenylsilyl (TBDPS), or trimethylacetyl (Piv). The key intermediate **18** was synthesized from *D*-ribose, as shown in Scheme 1.

D-Ribose was converted to a known cyclopentenone **12**, according to our previously published procedure.²¹ Iodination of **12** followed by reduction with NaBH₄ and protection of the resulting allylic alcohol with the TBDPS group afforded **13**.¹⁴ Because the benzyl protecting group gave better result than the Tr or TBDPS group in the electrophilic fluorination reaction,¹⁴



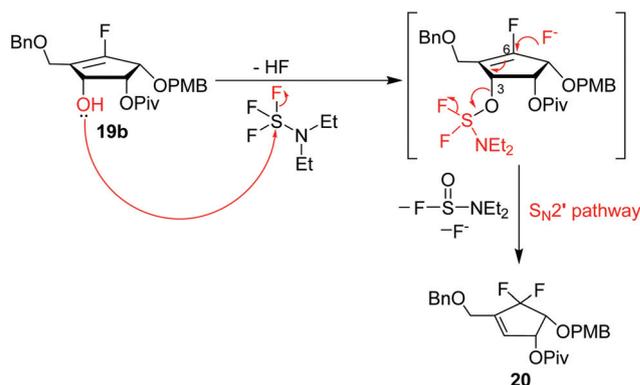
Scheme 1 Synthesis of the key intermediate **18**. Reagents and conditions: (a) I₂, pyridine, THF, rt, 4 h; (b) NaBH₄, CeCl₃·7H₂O, MeOH, 0 °C, 30 min; (c) TBDPSCl, imidazole, DMF, 40 °C, 12 h; (d) (CH₃)₃Al, MC, 0 °C to rt, 2 h; (e) BnBr, NaH, TBAI, DMF, rt, 3 h; (f) *N*-fluorobenzene sulfonimide, *n*-BuLi, THF, 78 °C, 1 h; (g) *n*-Bu₄NF, THF, rt, 2 h; (h) PMBCl, NaH, TBAI, DMF, rt, 3 h; (i) 2 N HCl/THF (1 : 1), 35 °C, 18 h.



Scheme 2 Synthesis of glycosyl donors **22** and **23** containing fluoro substituent. Reagents and conditions: (a) Piv-Cl, DIPEA, DMAP, CH_2Cl_2 , -10°C , 2 h; (b) DAST, pyridine, CH_2Cl_2 , 45°C , 18 h; (c) DDQ, CH_2Cl_2 , rt, 18 h.

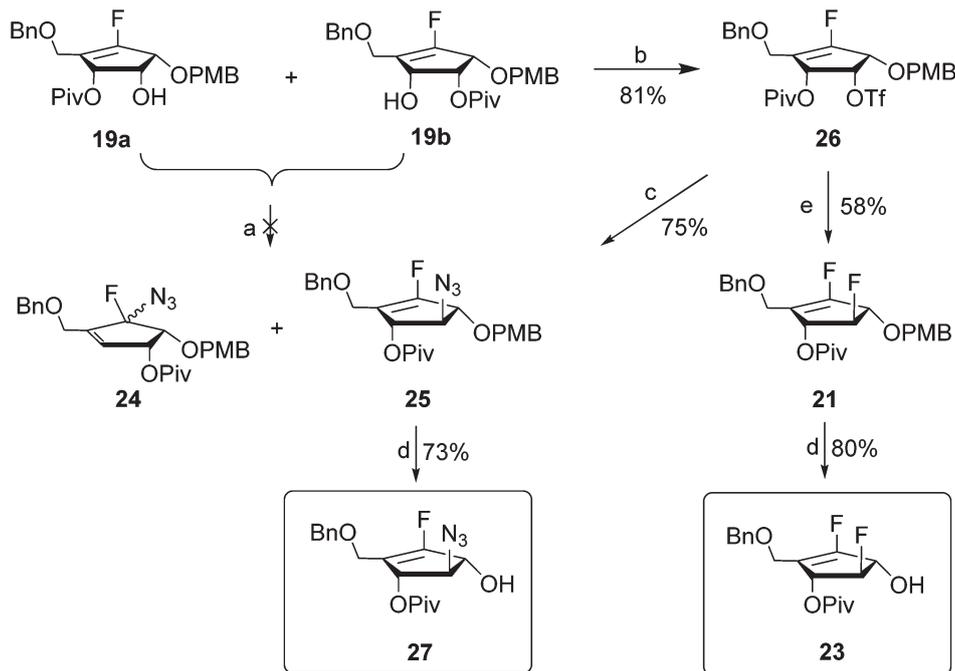
the trityl group was replaced with the benzyl group under mild conditions. Selective removal of the trityl group in **13** was achieved by using trimethylaluminium in the presence of acetone to give **14** which was again protected with the benzyl group to yield **15**. Compound **15** was converted to 6-fluoro derivative **16** via known procedures¹⁴ involving electrophilic fluorination with *n*-butyllithium and *N*-fluorobenzene sulfonamide (NFSI) followed by TBDPS deprotection. Treatment of **16** with *p*-methoxybenzyl chloride (PMB-Cl) afforded **17** which was subjected to acidic hydrolysis to give diol **18**, which is a good substrate for selective C2 functionalization.

To obtain desired regioselective protection at the 3'-hydroxyl group, diol **18** was protected with bulky protecting groups such as TBDPS, Tr, or Piv, but only the Piv group resulted in regioselective protection of the 3'-hydroxyl group over the 2'-hydroxyl group, giving the desired isomer **19a** and its regioisomer **19b** in a 5 : 1 ratio, which were very difficult to be separated by silica gel chromatography (Scheme 2). Treatment of a mixture of **19a** and **19b** with *N,N*-diethylaminosulfur trifluoride (DAST) yielded the desired 2'- β -fluoro analogue **21** (57%) as a major product along with geminal difluoro derivative **20** (14%) as a minor product. It is believed that the desired product **21** was directly generated from **19a** through $\text{S}_{\text{N}}2$ reaction, while difluoro derivative **20** was derived from **19b** via $\text{S}_{\text{N}}2'$ reaction, whose mechanism of action is illustrated in Scheme 3. This reaction gave the same results as that of each of isolated isomers **19a** and **19b**.



Scheme 3 Plausible mechanism for the formation of *gem*-difluoro derivative **20**.

In the first step, substrate **19b** reacted with DAST, forming an alkoxyaminosulfur difluoride intermediate. In the 2nd step, the fluoride attacked the C6 carbon of the intermediate via the $\text{S}_{\text{N}}2'$ mechanism, instead of direct $\text{S}_{\text{N}}2$ attack at the C3 carbon, resulting in the formation of *gem*-difluoro derivative **20**. Though compound **20** was an undesired product, its structural similarity to (–)-neplanocin F²⁰ inspired us to use this intermediate to develop a novel (–)-neplanocin F analogue. The structure of geminal difluoro derivative **20** was easily confirmed by $^1\text{H NMR}$, which shows a singlet at 6.0 ppm, corres-



Scheme 4 Stereo- and regioselective synthesis of 2'-β-azido glycosyl donor 27. Reagents and conditions: (a) DPPA, Ph₃P, THF, 0 °C to 60 °C; (b) Tf₂O, pyridine, rt, 1 h; (c) NaN₃, DMF, rt, 1 h; (d) DDQ, CH₂Cl₂, rt, 18 h; (e) TBAF, THF, rt, 12 h.

ponding to vinylic 3-H of 20. Further confirmation was provided by ¹⁹F NMR showing 2 peaks, one at -108.4 ppm and another at -109.3 ppm with the coupling constant 255.3 Hz, corresponding to *geminal* F,F coupling. Removal of the PMB group in compounds 20 and 21 with DDQ afforded the glycosyl donors 22 and 23, respectively.

Another glycosyl donor, 2'-β-azido derivative 27 was synthesized as shown in Scheme 4. We first tried the Mitsunobu reaction with diphenylphosphoryl azide (DPPA). However, the Mitsunobu reaction of a mixture of 19a and 19b with DPPA did not afford any desired S_N2' product 24 or S_N2 product 25, as depicted in Scheme 2. This might be attributed to difficulty in forming an alkoxy intermediate because of steric clashes between bulky protecting groups. Thus, we decided to utilize direct S_N2 displacement of the triflate with the azide. When a mixture of 19a and 19b was treated with triflic anhydride, only desired C2-triflate 26 was surprisingly obtained as a single regioisomer. The plausible mechanism for the sole formation of 26 is explained in Scheme 5.

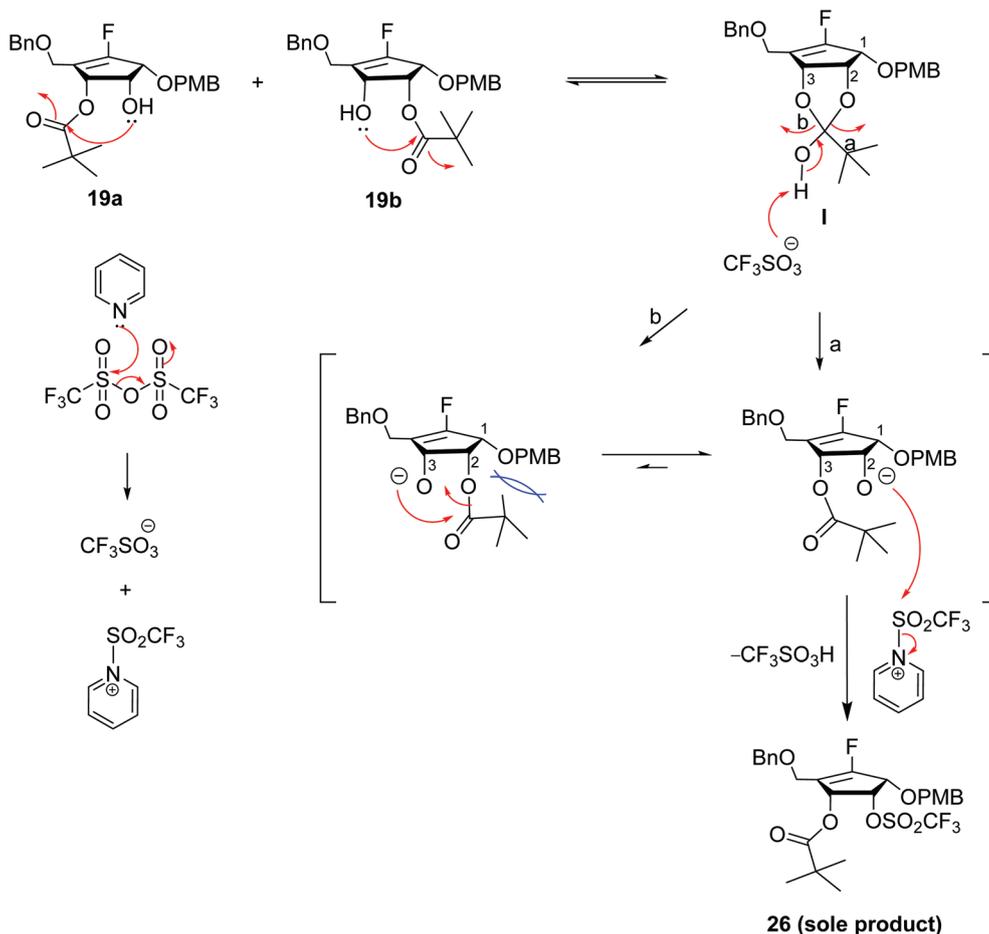
Compounds 19a and 19b are first equilibrated to form the common cyclic intermediate **I** by intramolecular attack of the hydroxyl group to carbonyl carbon of the pivaloyl moiety. The cyclic intermediate **I** is then opened up in two routes. Route a is much more favored than route b because of steric hindrance between PMB and Piv groups, affording desired derivative 26 as a sole regioisomer. The 2'-β-azido glycosyl donor 27 was then obtained *via* direct nucleophilic displacement of triflate 26 with sodium azide in DMF followed by the removal of the PMB group with DDQ. The same 2-β-fluoro glycosyl donor 23,

synthesized in Scheme 2 was also derived from triflate 26 by treating with *n*-tetrabutylammonium fluoride (TBAF) followed by the removal of the PMB group.

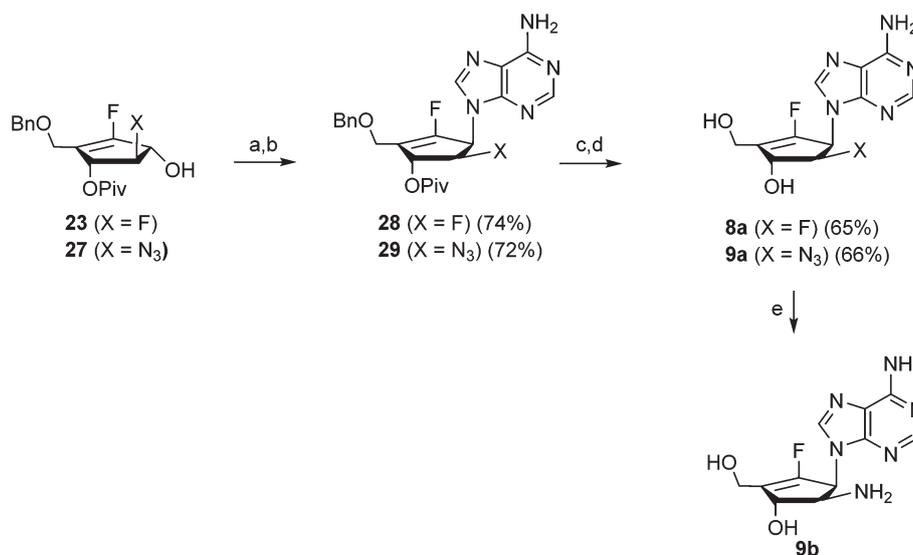
Syntheses of 2'-β-substituted purine nucleosides 8a, 9a, and 9b were accomplished using the Mitsunobu reaction as the key step (Scheme 6). Condensation of glycosyl donors 23 and 27 with 6-chloropurine under the standard Mitsunobu conditions yielded the N⁹-6-chloropurine derivatives [UV(CH₂Cl₂) λ_{max} 262 nm], which after a short flash silica gel column chromatography, were treated with *tert*-butanolic ammonia solution at 120 °C to afford adenosine derivatives 28 and 29, respectively. Treatment of 28 and 29 with 10% boron tribromide solution in methylene chloride followed by the removal of the pivaloyl group upon treatment with methanolic ammonia at 45 °C afforded the final nucleosides 8a and 9a, respectively. Compound 9a was further reduced to yield the 2'-β-amino-fluoroneplanocin A analogue 9b.

In a similar manner, *gem*-difluoro intermediate 22 was converted to the (-)-neplanocin F analogue 10, as shown in Scheme 7. Mitsunobu condensation of 22 with 6-chloropurine at 60 °C yielded the 6-chloro derivative 30, which was treated with *tert*-butanolic ammonia at 120 °C to furnish adenosine derivative 31. Subsequent removal of benzyl and pivaloyl protecting groups from 31 produced *gem*-difluoro nucleoside 10.

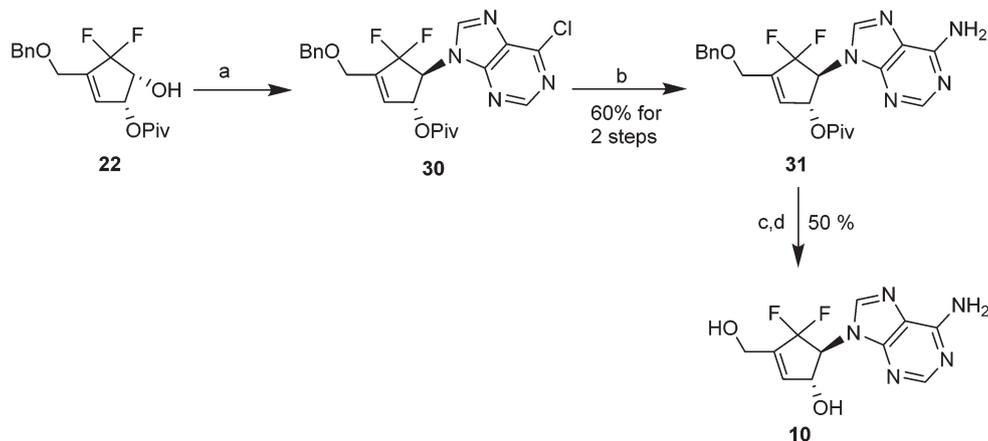
Synthesis of 2'-β-substituted pyrimidine nucleosides 8b-d and 9c-e is shown in Scheme 8. The 2'-β-fluoro glycosyl donor 23 was condensed with N³-benzoyluracil and -thymine under the Mitsunobu conditions and then treated with BBr₃ to give the 2'-β-fluoro derivatives 32 and 33, respectively. Removal of the



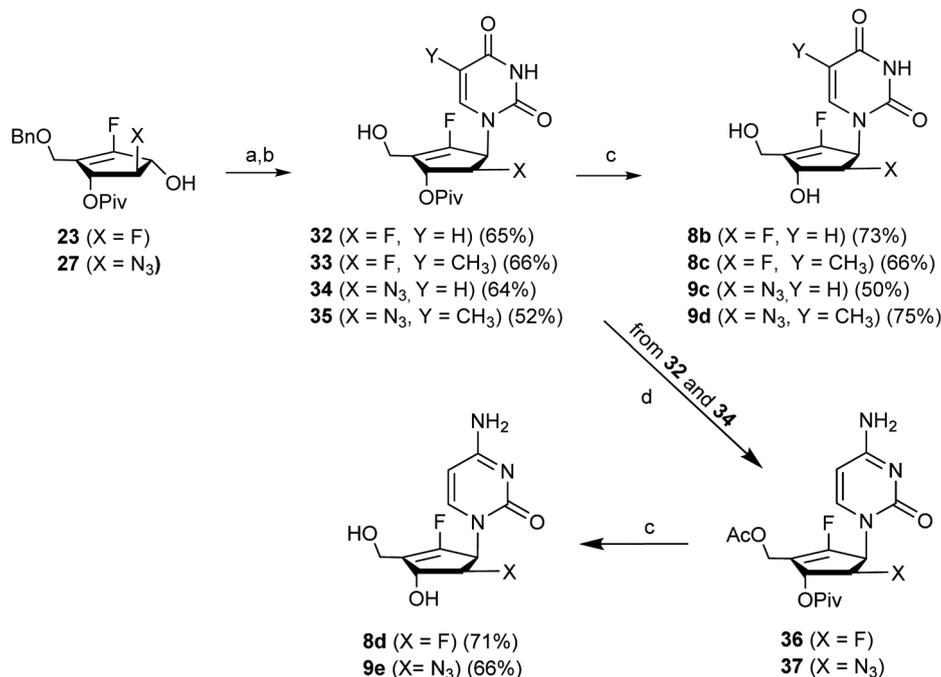
Scheme 5 Plausible mechanism for the sole formation of **26**.



Scheme 6 Synthesis of 2'- β -substituted purine nucleosides **8a**, **9a**, and **9b**. Reagents and conditions: (a) 6-chloropurine, DIAD, PPh₃, THF, rt, 18 h; (b) NH₃/tBuOH, 120 °C, sealed tube, 12 h; (c) BBr₃, CH₂Cl₂, -78 °C, 3 h; (d) NH₃/MeOH, 40 °C, 18 h; (e) PPh₃, NH₄OH, THF/H₂O, rt, 18 h.



Scheme 7 Synthesis of *gem*-difluoro substituted (–)-neplanocin F analogue **10**. Reagents and conditions: (a) 6-chloropurine, DIAD, PPh₃, THF, 60 °C, 18 h; (b) NH₃/tBuOH, 120 °C, sealed tube, 12 h; (c) BBr₃, CH₂Cl₂, –78 °C, 3 h; (d) NH₃/MeOH, 40 °C, 18 h.



Scheme 8 Synthesis of 2'- β -substituted pyrimidine nucleosides **8b–d** and **9c–e**. Reagents and conditions: (a) *N*³-benzoyluracil or *N*³-benzoylthymine, DIAD, PPh₃, THF, rt, 18 h; (b) BBr₃, MC, –78 °C, 3 h; (c) NH₃/MeOH, 40 °C, 15 h; (d) (i) Ac₂O, pyridine, rt, 2 h, (ii) POCl₃, 1,2,4-triazole, CH₃CN, 0 °C to rt, 18 h, (iii) NH₄OH/1,4-dioxane, rt, 15 h.

protecting groups of **32** and **33** yielded the uracil derivative **8b** and the thymine derivative **8c**. The 2'- β -azido glycosyl donor **27** was similarly converted to the uracil derivative **9c** and the thymine derivative **9d**. Uracil derivatives **32** and **34** were converted to the 2'- β -fluorocytosine derivative **8d** and 2'- β -azidocytosine derivative **9e**, respectively, by a conventional method.

All the synthesized 2'- β -substituted-fluoroneplanocin A analogues **8a–d** and **9a–e** and *gem*-difluoro (–)-neplanocin F analogue **10** were evaluated for their cytotoxic activity against several human cell lines such as human lung cancer cell line

(A549), human colon cancer cell line (HCT-116), human breast cancer cell line (MDA-MB-231), human prostate cancer cell line (PC3), human liver cancer cell line (SK-Hep-1), and human stomach cancer cell line (SNU-638).²² Unlike the 2'-hydroxyl derivatives **1–4**, showing potent antitumor activities, all of the synthesized compounds did not exhibit promising anticancer activity up to 100 μ M, indicating that the 2'-hydroxyl group is essential for biological activity in this series. The change of the sugar conformation from the *ribo* configuration to the *arabino* or 2-*deoxyribo* configuration might decrease the favorable

interaction between the compound and the cellular polymerase, resulting in a loss of biological activity.

Conclusions

In summary, a series of 2'- β -substituted-fluoroneplanocin A analogues **8** and **9** were successfully synthesized from D-ribose in a regio- and stereoselective manner. During the introduction of a 2'- β -fluoro group with DAST, unusual geminal-difluoro product **20** was formed *via* the S_N2' reaction along with the desired 2'- β -fluoro derivative **21**. It was discovered that triflation of the 2-hydroxyl or 3-hydroxyl group with the neighboring pivaloyl acyl group resulted in the sole formation of C2-triflate **26** because of steric effects between protecting groups. This triflate **26** was utilized for the regio- and stereoselective synthesis of 2'- β -azido- and 2'- β -fluoro derivatives by treating with sodium azide and *n*-tetrabutylammonium fluoride, respectively. All glycosyl donors **22**, **23**, and **27** were converted to the pyrimidine and purine nucleosides using the Mitsunobu reaction as the key step. However, none of the synthesized compounds showed significant biological activities. Despite lack of biological activities, it is believed that this study will greatly contribute to understanding the essential structural requirements for biological activities of this class of carbocyclic nucleosides. This in turn will contribute to the design and synthesis of novel antitumor nucleosides.

Experimental section

General methods

¹H NMR spectra (CDCl₃, CD₃OD, or DMSO-*d*₆) were recorded on a Varian Unity Inova 400 MHz instrument. The ¹H NMR data are reported as peak multiplicities: s for singlet, d for doublet, dd for doublet of doublets, t for triplet, q for quartet, br s for broad singlet, and m for multiplet. Coupling constants are reported in hertz. ¹³C NMR spectra (CDCl₃, CD₃OD, or DMSO-*d*₆) were recorded on a Varian Unity Inova 100 MHz instrument. ¹⁹F NMR spectra (CDCl₃ or CD₃OD) were recorded on a Varian Unity Inova 376 MHz instrument. The chemical shifts were reported as parts per million (δ) relative to the solvent peak. Optical rotations were determined on Jasco III in an appropriate solvent. UV spectra were recorded on U-3000 made by Hitachi in methanol or water. Infrared spectra were recorded on FT-IR (FTS-135) made by Bio-Rad. Melting points were determined on a Buchan B-540 instrument and are uncorrected. Reactions were checked with TLC (Merck pre-coated 60F254 plates). Flash column chromatography was performed on silica gel 60 (230–400 mesh, Merck). Reagents were purchased from Aldrich Chemical Co. Solvents were obtained from local suppliers. All the anhydrous solvents used were redistilled over CaH, P₂O₅, or sodium/benzophenone prior to the reaction.

((3*aR*,4*R*,6*aR*)-*tert*-Butyl-5-iodo-2,2-dimethyl-6-(trityloxymethyl)-4,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yloxy)diphenyl-

silane (13).²³ To a stirred solution of **12** (42.0 g, 98.47 mmol) in anhydrous THF (450 mL) at -10 °C was added iodine (87.5 g, 344.7 mmol) portionwise followed by pyridine (56 mL, 393.88 mmol) under a N₂ atmosphere and the resulting solution was stirred at room temperature for 4 h. The reaction mass was quenched with saturated sodium thiosulfate solution at 0 °C until the solution becomes colorless. The aqueous portion was extracted with ethyl acetate (500 mL). The organic layer was further washed with water (200 mL), brine (200 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The residue obtained was purified by flash silica gel column chromatography (hexane:EtOAc = 7:1) to give ketone (38.0 g, 70%) as a white foam. To a solution of ketone (38.0 g, 68.79 mmol) in methanol (400 mL) were added cerium(III) chloride heptahydrate (28.2 g, 75.67 mmol) and sodium borohydride (2.82 g, 75.67 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with water (250 mL) and partially concentrated under reduced pressure to remove methanol. The aqueous portion was extracted with ethyl acetate (250 mL \times 2). The organic layer was washed with brine (150 mL \times 2), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to give α -hydroxy intermediate (25.0 g) as a yellow syrup.

To a stirred solution of α -hydroxy intermediate (25.0 g, 45.11 mmol) in anhydrous DMF (250 mL) were added imidazole (9.21 g, 135.35 mmol) and TBDPSCl (28.72 mL, 112.79 mmol) at 0 °C under nitrogen. The resulting solution was stirred at room temperature for 16 h, quenched with water (200 mL), and extracted with diethyl ether (200 mL \times 2). The combined organic layers were dried over anhydrous MgSO₄, filtered, and evaporated. The crude residue obtained was purified by flash silica gel column chromatography (hexane:EtOAc = 15:1) to give **13**²³ (32.5 g, 90%) as a white foam: ¹H NMR (CDCl₃, 400 MHz) δ 1.15 (s, 9H), 1.27 (s, 3H), 1.31 (s, 3H), 3.80 (d, *J* = 11.6 Hz, 1H), 3.91 (d, *J* = 11.6 Hz, 1H), 4.07 (t, *J* = 5.6 Hz, 1H), 4.48 (d, *J* = 4.4 Hz, 1H), 4.95 (d, *J* = 5.6 Hz, 1H), 7.20–7.50 (m, 21H), 7.81–7.84 (m, 4H).

((3*aR*,6*R*,6*aR*)-6-(*tert*-Butyldiphenylsilyloxy)-5-iodo-2,2-dimethyl-6,6*a*-dihydro-3*aH*-cyclopenta[*d*][1,3]dioxol-4-yl)methanol (14). To a stirred solution of **13** (30.00 g, 37.84 mmol) in anhydrous methylene chloride (300 mL) was added trimethylaluminum (47.3 mL, 94.59 mmol) dropwise at -10 °C under nitrogen and the resulting solution was slowly allowed to reach room temperature and stirred for an additional 2 h. The reaction mixture was cooled to 0 °C, quenched with ammonium chloride (200 mL) slowly and extracted with methylene chloride (150 mL \times 2). The combined organic layers were washed with brine (100 mL \times 2), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (hexane:EtOAc = 3:1) to give **14** (18.00 g, 86%) as a white foam: $[\alpha]_D^{25} = +6.1$ (*c* 5.0, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 1.16 (s, 3H), 1.22 (s, 3H), 1.40 (s, 9H), 4.04 (t, *J* = 5.2 Hz, 1H), 4.28–4.40 (m, 2H), 4.52–4.54 (m, 1H), 4.80 (d, *J* = 5.6 Hz, 1H), 7.30–7.47 (m, 6 H), 7.81–7.85 (m, 4 H); ¹³C NMR (CDCl₃,

100 MHz) δ 19.8, 26.7, 27.3, 27.6, 62.6, 71.0, 75.9, 79.0, 83.1, 105.5, 112.1, 127.5, 127.7, 128.0, 128.2, 129.9 (d, $J = 3.9$ Hz), 133.7, 134.1, 136.1, 136.6, 136.7; MS (ESI⁺): Calculated: 573.0934 for C₂₅H₃₁IO₄SiNa (M + Na)⁺, found: 573.0926.

((3aR,4R,6aR)-6-(Benzyloxymethyl)-5-iodo-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-yloxy)(tert-butyl)diphenylsilane (15).¹⁴ To a stirred suspension of sodium hydride (6.5 g, 163.48 mmol, 60% dispersion in mineral oil) in THF (100 mL) was added a solution of **14** (18.00 g, 32.7 mmol) in THF (100 mL) at 0 °C and the mixture was stirred at room temperature for 30 min. To this solution, tetrabutylammonium iodide (6.0 g, 16.35 mmol) and benzyl bromide (5.81 mL, 49.05 mmol) were added at 0 °C and the reaction mixture was continued to be stirred at room temperature for 4 h and then slowly poured into ice cold water (150 mL). The solution was further diluted with water (100 mL) and extracted with ethyl acetate (100 mL \times 2). The combined organic layers were washed with sodium thiosulfate solution (100 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : EtOAc = 9 : 1) to give **15** (19.0 g, 95%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 1.12 (s, 9H), 1.23 (s, 3H), 1.36 (s, 3H), 4.03 (t, $J = 5.6$ Hz, 1H), 4.18 (d, $J = 11.6$ Hz, 1H), 4.25 (d, $J = 11.6$ Hz, 1H), 4.47 (d, $J = 12.0$ Hz, 1H), 4.51 (d, $J = 5.6$ Hz, 1H), 4.53 (d, $J = 12.0$ Hz, 1H), 4.77 (d, $J = 5.6$ Hz, 1H), 7.34 (m, 11H), 7.82 (m, 4H); ¹³C NMR (CDCl₃, 100 MHz) δ 19.8, 26.9, 27.3, 27.6, 68.2, 73.1, 77.5, 79.2, 82.4, 108.2, 111.9, 127.5, 127.7, 127.8, 127.9, 128.5, 129.9, 133.0, 134.1, 136.7, 136.7, 138.3, 144.9. Remaining data matched with the earlier report.¹⁴

(3aS,4R,6aR)-6-(Benzyloxymethyl)-5-fluoro-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (16).¹⁴ To a stirred solution of **15** (2.85 g, 4.45 mmol) and *N*-fluorobenzene sulfonimide (2.1 g, 6.67 mmol) in dry THF (40 mL) was added *n*-butyllithium (8.34 mL, 13.35 mmol, 1.6 M solution in hexanes) dropwise at -78 °C under a N₂ atmosphere and the resulting solution was stirred at the same temperature for an additional 1 h. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) and extracted with ethyl acetate (25 mL \times 2). The combined organic layers were washed with brine solution (30 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (hexane : EtOAc = 30 : 1) to give an inseparable mixture of 5-F and 5-H derivatives (1.8 g) as a colorless oil. To a stirred solution of a mixture of above derivatives (1.8 g, 3.38 mmol) in THF (25 mL) was added tetrabutylammonium fluoride (5 mL, 1.69 mmol, 1.0 M solution in THF) at 0 °C and the mixture was stirred at room temperature for 2 h and evaporated. The crude residue was purified by flash silica gel column chromatography (hexane : EtOAc = 5 : 1) to give **16**¹⁴ (0.85 g, 65% for 2 steps) as a colorless syrup and 5-H derivative (0.1 g, 8% for 2 steps) as a colorless syrup:

Compound 16. [α]_D²⁵ = +42.3 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 1.42 (s, 3H), 1.46 (s, 3H), 2.83 (d, $J = 8.4$ Hz, 1H), 4.06–4.10 (m, 1H), 4.30 (d, $J = 12.0$ Hz, 1H), 4.47–4.58 (m, 3H), 4.69 (superimposed ddd, $J = 3.6, 6.0, 9.6$ Hz, 1H), 5.06 (pseudo

t, $J = 6.0, 7.2$ Hz, 1H), 7.26–7.42 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 26.5, 27.8, 61.3, 69.3 (d, $J = 8.4$ Hz), 73.1, 74.0 (d, $J = 7.6$ Hz), 78.6 (d, $J = 10.0$ Hz), 112.7, 115.3 (d, $J = 5.4$ Hz), 128.0, 128.6, 138.1, 157.8, 159.2 (d, $J = 288.4$ Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -129.3; MS (ESI): Calculated: 295.1346 for C₁₆H₂₀FO₄ (M + H)⁺, found: 295.1342.

(3aR,4R,6aR)-6-(Benzyloxymethyl)-5-fluoro-4-(4-methoxybenzyloxy)-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxole (17). To a stirred ice cooled solution of **16** (2.8 g, 9.51 mmol) in DMF (30 mL) was added sodium hydride (1.52 g, 38.05 mmol, 60% dispersion in mineral oil) portionwise at 0 °C and the mixture was stirred at room temperature under a N₂ atmosphere for 30 min. To this resulting solution, tetrabutylammonium iodide (1.76 g, 4.76 mmol) and 4-methoxybenzyl chloride (1.55 mL, 11.42 mmol) were added at 0 °C and the mixture was allowed to stir at the same temperature for 15 min, later at room temperature for 3 h. The reaction mixture was carefully poured into ice-cold water (50 mL) and extracted with EtOAc (30 mL \times 2). The combined organic layers were washed with sodium thiosulfate solution (50 mL), dried over anhydrous MgSO₄, filtered and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (hexane : EtOAc = 9 : 1) to give **17** (3.17 g, 81%) as a thick yellow syrup: [α]_D²⁵ = -3.23 (*c* 2.1, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 1.42 (s, 3H), 1.48 (s, 3H), 3.81 (s, 3H), 4.07–4.11 (m, 1H), 4.30–4.32 (m, 2H), 4.47–4.61 (m, 3H), 4.69 (superimposed ddd, $J = 3.2, 5.6, 8.8$ Hz, 1H), 4.77 (d, $J = 11.2$ Hz, 1H), 5.00 (dd, $J = 6.0, 6.4$ Hz, 1H), 6.88–6.91 (m, 2H), 7.26–7.35 (m, 7H); ¹³C NMR (100 MHz, CDCl₃) δ 26.8, 27.7, 55.4, 61.3, 71.9, 72.9, 74.8 (d, $J = 7.3$ Hz), 75.0 (d, $J = 18.3$ Hz), 78.5 (d, $J = 9.6$ Hz), 112.7, 114.0, 116.1 (d, $J = 4.4$ Hz), 127.8, 127.9, 128.5, 129.8, 130.0, 138.1, 157.8 (d, $J = 289.2$ Hz), 159.5; ¹⁹F NMR (376 MHz, CDCl₃) δ -126.8; MS (ESI): Calculated: 437.1740 for C₂₄H₂₇FNao₅ (M + Na)⁺, found: 437.1687.

(1R,2R,5R)-3-(Benzyloxymethyl)-4-fluoro-5-(4-methoxybenzyloxy)cyclopent-3-ene-1,2-diol (18). A solution of **17** (0.5 g, 1.21 mmol) in 2 N HCl/THF (1 : 1) (5 mL) was stirred at 30 °C for 18 h. The reaction mixture was neutralized with saturated NaHCO₃ (5 mL) solution, diluted with water (10 mL) and extracted with EtOAc (15 mL \times 3). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash silica gel column chromatography (hexane : EtOAc = 1.5 : 1) to give **18** (0.35 g, 78%) as a white solid: [α]_D²⁵ = +62.66 (*c* 0.3, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 2.76 (d, $J = 6.8$ Hz, 1H), 3.24 (d, $J = 8.4$ Hz, 1H), 3.80 (s, 3H), 4.07–4.18 (m, 2H), 4.21–4.24 (m, 2H), 4.46–4.56 (m, 3H), 4.70 (s, 2H), 6.88–6.91 (m, 2H), 7.26–7.35 (m, 7H); ¹³C NMR (100 MHz, CDCl₃) δ 55.4, 61.5, 67.8 (d, $J = 7.7$ Hz), 71.4 (d, $J = 7.8$ Hz), 73.0, 73.1, 75.9 (d, $J = 19.4$ Hz), 114.1, 119.3 (d, $J = 3.1$ Hz), 128.0, 128.6, 129.4, 129.9, 138.0, 159.5 (d, $J = 287.9$ Hz), 159.7; ¹⁹F NMR (376 MHz, CDCl₃) δ -126.1; MS (ESI⁺): Calculated: 397.1427 for C₂₁H₂₃FNao₅ (M + Na)⁺, found: 397.1391.

(1R,4R,5R)-2-(Benzyloxymethyl)-3-fluoro-5-hydroxy-4-(4-methoxybenzyloxy)cyclopent-2-enyl pivalate (19a) and (1R,2R,5R)-3-

(benzyloxymethyl)-4-fluoro-2-hydroxy-5-(4-methoxybenzyloxy)-cyclopent-3-enyl pivalate (**19b**). To a stirred solution of **18** (1.26 g, 3.37 mmol) in methylene chloride (20 mL) were added DMAP (0.062 g, 0.15 mmol), DIPEA (1.75 mL, 10.1 mmol), and trimethylacetyl chloride (0.45 mL, 3.7 mmol) at $-10\text{ }^{\circ}\text{C}$ and the resulting solution was stirred at the same temperature for an additional 2 h and quenched with saturated NaHCO_3 (15 mL) solution. The aqueous phase was extracted with methylene chloride (15 mL \times 2). The combined organic layers were washed with brine (20 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue obtained was purified by flash silica gel column chromatography (hexane : EtOAc = 9 : 1) to give **19a** and **19b** as a 5 : 1 inseparable mixture as predicted by ^1H NMR.

(1*R*,5*R*)-3-(Benzyloxymethyl)-4,4-difluoro-5-(4-methoxybenzyloxy)cyclopent-2-enyl pivalate (**20**) and (1*R*,4*R*,5*S*)-2-(benzyloxymethyl)-3,5-difluoro-4-(4-methoxybenzyloxy)cyclopent-2-enyl pivalate (**21**). To a stirred solution of **19a** and **19b** (0.37 g, 0.8 mmol) in methylene chloride (10 mL) were added pyridine (0.26 mL, 3.19 mmol) and DAST (0.37 mL, 2.79 mmol) at $0\text{ }^{\circ}\text{C}$ and the reaction mixture was heated to $45\text{ }^{\circ}\text{C}$ for 18 h. The reaction mixture was cooled to room temperature, quenched with saturated NaHCO_3 (10 mL) solution and extracted with methylene chloride (10 mL \times 2). The combined organic layers were washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (hexane : EtOAc = 9 : 1) to yield **20** (0.05 g, 14%) and **21** (0.21 g, 57%) as thick yellow syrups.

Compound 20. $[\alpha]_{\text{D}}^{25} = -55.04$ (*c* 4.5, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 1.14 (s, 9H), 3.80 (s, 3H), 4.09–4.28 (m, 3H), 4.54–4.57 (m, 3H), 4.68 (d, *J* = 11.2 Hz, 1H), 5.62–5.64 (m, 1H), 6.24–6.25 (m, 1H), 6.84–6.87 (m, 2H), 7.24–7.38 (m, 7H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 27.3, 39.0, 55.4, 64.0, 70.6 (d, *J* = 8.6 Hz), 73.1, 73.3, 78.04–78.51 (m), 113.9, 127.9, 128.1, 128.7, 129.4, 129.9, 132.0 (t, *J* = 8.6 Hz), 137.7, 142.1 (t, *J* = 24.4 Hz), 160.0, 178.2; ^{19}F NMR (CDCl_3 , 400 MHz), δ -108.4 (dt, $J_{\text{C-F}} = 7.5$, 255.3 Hz, 1F), -109.2 (dd, $J_{\text{C-F}} = 10.2$, 255.3 Hz, 1F); MS (ESI^+): Calculated: 483.1959 for $\text{C}_{26}\text{H}_{30}\text{F}_2\text{NaO}_5$ ($\text{M} + \text{Na}^+$), found: 483.1908.

Compound 21. $[\alpha]_{\text{D}}^{25} = +10.15$ (*c* 4.5, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 1.18 (s, 9H), 3.80 (s, 3H), 3.90–3.94 (m, 1H), 4.17 (d, *J* = 12.4 Hz, 1H), 4.42–4.54 (m, 3H), 4.65 (d, *J* = 11.2 Hz, 2H), 4.84 (d, $J_{\text{F-H}} = 50.0$ Hz, 1H), 5.71–5.78 (m, 1H), 6.88–6.91 (m, 2H), 7.24–7.35 (m, 7H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 27.2, 39.0, 55.5, 60.5, 72.3, 73.0, 75.2 (dd, *J* = 8.1, 30.1 Hz), 80.1 (dd, *J* = 19.8, 27.9 Hz), 100.2 (dd, $J_{\text{C-F}} = 192.3$, 7.3 Hz), 114.2, 115.2 (m), 128.0, 128.6, 129.1, 129.9, 137.7, 156.7 (dd, $J_{\text{C-F}} = 8.1$, 288.5 Hz), 159.8, 177.6; ^{19}F NMR (376 MHz, CDCl_3) δ -123.1 , -185.7 ; MS (ESI^+): Calculated: 483.1959 for $\text{C}_{26}\text{H}_{30}\text{F}_2\text{NaO}_5$ ($\text{M} + \text{Na}^+$), found: 483.1916.

General procedure for PMB deprotection

To a stirred solution of PMB protected derivative **20** or **21** (1 equiv.) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (10 : 1) was added DDQ (2 equiv.) at room temperature and the reaction mixture was stirred at

room temperature for 18 h. The reaction mixture was quenched with saturated NaHCO_3 solution and extracted with methylene chloride twice. The combined organic layers were washed with brine and water, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The residue obtained was purified by flash silica gel column chromatography (hexane : EtOAc = 4 : 1) to yield the hydroxy derivative **22** or **23**, respectively.

(1*R*,5*R*)-3-(Benzyloxymethyl)-4,4-difluoro-5-hydroxycyclopent-2-enyl pivalate (**22**). Yellow syrup. Yield: 82%; $[\alpha]_{\text{D}}^{25} = -62.8$ (*c* 5.07, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 1.22 (s, 9H), 1.57 (br s, 1H), 2.37 (dd, *J* = 2.4, 10.4 Hz), 4.19–4.40 (m, 3H), 4.58–4.59 (m, 2H), 5.48–5.51 (m, 1H), 6.35–6.37 (m, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 21.7, 27.8, 39.0, 55.4, 64.0, 71.3 (dd, *J* = 1.8, 12.2 Hz), 72.6, 72.8 (d, *J* = 7.1 Hz), 73.1, 122.7 (d, *J* = 248.7 Hz), 127.7, 127.9, 128.5, 131.9 (m), 137.4, 142.6 (dd, *J* = 22.8, 25.7 Hz), 165.2, 168.5, 177.5; ^{19}F NMR (CDCl_3 , 400 MHz), δ -108.4 (dt, $J_{\text{C-F}} = 7.5$, 255.3 Hz, 1F), -109.2 (dd, $J_{\text{C-F}} = 10.2$, 255.3 Hz, 1F); MS (ESI^+): Calculated: 363.1384 for $\text{C}_{18}\text{H}_{22}\text{F}_2\text{NaO}_4$ ($\text{M} + \text{H}^+$), found: 363.1382.

(1*R*,4*R*,5*R*)-2-(Benzyloxymethyl)-3,5-difluoro-4-hydroxycyclopent-2-enyl pivalate (**23**). Yellow syrup. Yield: 80%; $[\alpha]_{\text{D}}^{25} = -2.8$ (*c* 1.82, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 1.17 (s, 9H), 3.24 (d, *J* = 6.8 Hz, 1H), 3.91–3.95 (m, 1H), 4.17 (d, *J* = 12.1 Hz, 1H), 4.47 (dd, $J_{\text{AB}} = 12.1$ Hz, 2H), 4.67–4.74 (m, 1H), 4.82 (d, $J_{\text{H-F}} = 50.0$ Hz, 1H), 5.60–5.68 (m, 1H), 7.25–7.36 (m, 5H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 27.1, 39.0, 60.5, 73.0, 74.4 (dd, *J* = 21.7, 29.5 Hz), 75.7 (dd, *J* = 7.7, 31.0 Hz), 101.1 (dd, $J_{\text{C-F}} = 7.3$, 200.0 Hz), 114.3 (d, *J* = 3.9, 7.0 Hz), 128.1, 128.6, 137.6, 157.5 (dd, $J_{\text{C-F}} = 7.8$, 288.0 Hz), 178.1; ^{19}F NMR (376 MHz, CDCl_3) δ -129.3 , -190.8 ; MS (ESI^+): Calculated: 363.1384 for $\text{C}_{18}\text{H}_{22}\text{F}_2\text{NaO}_4$ ($\text{M} + \text{Na}^+$), found: 363.1377.

(1*R*,4*R*,5*R*)-2-(Benzyloxymethyl)-3-fluoro-4-(4-methoxybenzyloxy)-5-(trifluoromethyl sulfonyloxy)cyclopent-2-enyl pivalate (**26**). To a stirred solution of **19a** and **19b** (0.05 g, 0.11 mmol) in pyridine (2 mL) was added trifluoromethanesulphonic anhydride (0.037 mL, 0.22 mmol) dropwise at $0\text{ }^{\circ}\text{C}$ and the mixture was stirred for an additional 30 min. The reaction mixture was quenched with saturated NaHCO_3 (5 mL) solution and extracted with methylene chloride (10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The resulting residue was taken for the next step as such immediately. For analytical purpose the residue was purified by short flash silica gel column chromatography (hexane : EtOAc = 10 : 1) to give **26** (0.05 g, 81%) as a yellow syrup: ^1H NMR (CDCl_3 , 400 MHz) δ 1.17 (s, 9H), 3.80 (s, 3H), 3.96 (dd, *J* = 2.8, 12 Hz, 1H), 4.21 (d, *J* = 12.4 Hz, 1H), 4.43–4.51 (m, 3H), 4.65 (dd, *J* = 11.2, 11.6 Hz, 2H), 5.10 (t, *J* = 6.0 Hz, 1H), 5.90 (t, *J* = 5.6 Hz, 1H), 6.86–6.89 (m, 2H), 7.25–7.40 (m, 7H).

Alternative synthesis of **21**

To a stirred solution of **26** (1.5 g, 2.54 mmol) in THF (30 mL) was added tetrabutylammonium fluoride (5.08 mL, 5.08 mmol, 1.0 M solution in THF) at room temperature under

a N₂ atmosphere and the resulting solution was stirred at room temperature for 12 h. The reaction mixture was evaporated and the crude residue was purified by flash silica gel column chromatography (hexane:EtOAc = 9:1) to yield **21** (0.68 g, 58%) as a thick yellow syrup, whose spectroscopic data were identical to those of the authentic sample.

(1R,4R,5S)-5-Azido-2-(benzyloxymethyl)-3-fluoro-4-(4-methoxybenzyloxy)cyclopent-2-enyl pivalate (25). To a stirred solution of **26** (3.0 g, 5.08 mmol) in DMF (30 mL) was added sodium azide (0.49 g, 7.61 mmol) portionwise at room temperature under a N₂ atmosphere and the resulting solution was stirred at the same temperature for an additional 3 h. The reaction mixture was quenched with water (50 mL) and then extracted with EtOAc (25 mL × 2). The combined organic layers were washed with brine (2 × 25 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel column chromatography (hexane:EtOAc = 15:1) to give **25** (1.85 g, 75%) as a yellow syrup. [α]_D²⁵ = +49.4 (c 1.75, CH₂Cl₂); IR (film) 2105.2 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.18 (s, 9H), 3.82 (s, 4H), 3.93–3.96 (m, 1H), 4.18 (d, *J* = 12.0 Hz, 1H), 4.26 (t, *J* = 2.8 Hz, 1H), 4.46 (dd, *J* = 11.6, 12.0 Hz, 2H), 4.65 (dd, *J* = 11.2, 11.6 Hz, 2H), 5.57 (dd, *J* = 3.2, 7.6 Hz, 1H), 6.89–6.92 (m, 2H), 7.26–7.37 (m, 7H); ¹³C NMR (CDCl₃, 100 MHz) δ 27.1, 39.0, 55.5, 60.6, 70.40 (d, *J* = 27.6 Hz), 72.6, 75.5 (d, *J* = 7.7 Hz), 80.5 (d, *J* = 19.4 Hz), 114.2, 115.3 (d, *J* = 7.0 Hz), 128.0, 128.0, 128.1, 128.6, 129.2, 129.9, 137.7, 157.7 (d, *J*_{C-F} = 287.9 Hz), 159.8, 177.7; ¹⁹F NMR (376 MHz, CDCl₃) δ -123.5; MS (ESI⁺): Calculated: 506.2067 for C₂₆H₃₀FN₃NaO₅ (M + Na)⁺, found: 506.2005.

(1R,4R,5R)-5-Azido-2-(benzyloxymethyl)-3-fluoro-4-hydroxycyclopent-2-enylpivalate (27). Compound **25** was converted to **27** according to the same procedure used for the synthesis of **22** and **23**. Yield: 73%; [α]_D²⁵ = +57.7 (c 1.8, CH₂Cl₂); IR (film) 2109.2 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.19 (s, 9H), 2.85 (s, 1H), 3.81–3.83 (m, 1H), 3.93–3.97 (m, 1H), 4.16 (d, *J* = 12.0 Hz, 1H), 4.43–4.51 (m, 3H), 5.56–5.58 (m, 1H), 7.26–7.37 (m, 5H); ¹³C NMR (CDCl₃, 100 MHz) δ 27.1, 60.6, 72.0 (d, *J* = 6.9 Hz), 73.1, 75.5 (d, *J* = 7.7 Hz), 114.6 (d, *J* = 7.0 Hz), 128.1, 128.1, 128.7, 137.6, 157.7 (d, *J*_{C-F} = 287.1 Hz), 159.8, 178.0; ¹⁹F NMR (376 MHz, CDCl₃) δ -126.0; MS (ESI⁺): Calculated: 386.1492 for C₁₈H₂₂FN₃NaO₄ (M + Na)⁺, found: 386.1485.

General procedure for Mitsunobu condensation and amination

Mitsunobu condensation. Diisopropylazidocarboxylate (DIAD) (9.16 mmol) in THF was added to a stirred solution of 6-chloropurine or pyrimidine base (4.4 mmol) and triphenylphosphine (Ph₃P) (4.4 mmol) in anhydrous THF under N₂ at 0 °C and the mixture was stirred at the same temperature for 15 min. To this mixture was added a solution of glycosyl donor **22**, **23** or **27** (2.93 mmol) in THF and the reaction mixture was allowed to warm to room temperature and stirred for an additional 16 h. The reaction mixture was concentrated under reduced pressure and the crude residue obtained was purified by short flash silica gel column chromatography to give a

condensed product, which was taken for next step with DIAD impurities.

Amination. A solution of the condensed product (1 equiv.) in saturated NH₃/tBuOH (10 mL) was stirred at 110 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was further purified by flash silica gel column chromatography (CH₂Cl₂:MeOH = 30:1) to yield adenine derivative **28**, **29**, or **31**.

(1R,4S,5R)-4-(6-Amino-9H-purin-9-yl)-2-(benzyloxymethyl)-3,5-difluoro-cyclopent-2-enyl pivalate (28). Yellow foam. Yield: 74% (for 2 steps); UV (CH₂Cl₂) λ _{max} 257 nm; [α]_D²⁵ = -161 (c 0.2, CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ 1.20 (s, 9H), 4.12–4.16 (m, 1H), 4.33 (d, *J* = 12.4 Hz, 1H), 4.60 (dd, *J* = 11.6, 12.0 Hz, 2H), 5.25 (d, *J*_{H-F} = 49.6 Hz, 1H), 6.13–6.21 (m, 2H), 7.30–7.38 (m, 5H), 8.07 (s, 1H), 8.17 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 27.3, 27.4, 27.9, 39.8, 56.9 (t, *J* = 19.8 Hz), 61.4, 73.8, 78.7 (dd, *J* = 8.4, 29.0 Hz), 91.5 (dd, *J*_{C-F} = 5.3, 196.8 Hz), 118.7, 120.0, 129.0, 129.1, 129.4, 139.0, 142.0, 151.2, 154.2, 154.7 (d, *J*_{C-F} = 285.3 Hz), 157.4, 178.9; ¹⁹F NMR (376 MHz, CDCl₃) δ -121.3, -192.2; MS (ESI⁺): Calculated: 458.2004 for C₂₃H₂₆F₂N₅O₃ (M + H)⁺, Found: 458.1997.

(1R,4S,5R)-4-(6-Amino-9H-purin-9-yl)-5-azido-2-(benzyloxymethyl)-3-fluoro-cyclopent-2-enyl pivalate (29). Yellow syrup. Yield: 72% (for 2 steps); UV (MeOH) λ _{max} 260 nm; [α]_D²⁵ = +14.7 (c 1.75, CH₂Cl₂); IR (KBr) 2110.4 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 1.20 (s, 9H), 4.12–4.16 (m, 1H), 4.33 (d, *J* = 12.4 Hz, 1H), 4.60 (dd, *J* = 11.6, 12.0 Hz, 2H), 5.25 (d, 1H), 6.13–6.21 (m, 2H), 7.30–7.38 (m, 5H), 8.07 (s, 1H), 8.17 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 27.3, 27.4, 27.9, 39.8, 56.9, 61.4, 73.8, 78.7, 91.5, 118.7, 120.0, 129.0, 129.1, 129.4, 139.0, 142.0, 151.2, 154.2, 154.7 (d, *J*_{C-F} = 285.3 Hz), 157.4, 178.9; ¹⁹F NMR (376 MHz, CDCl₃) δ -121.3; MS (ESI⁺): Calculated: 481.2112 for C₂₃H₂₆FN₈O₃ (M + H)⁺, Found: 481.2110.

(1R,5S)-5-(6-Amino-9H-purin-9-yl)-3-((benzyloxy)methyl)-4,4-difluorocyclopent-2-enyl pivalate (31). White solid. Yield: 60% (for 2 steps); UV (MeOH) λ _{max} 259 nm; [α]_D²⁵ = +54.4 (c 1.8, MeOH); ¹H NMR (CD₃OD, 400 MHz) δ 4.31 (s, 2H), 4.62 (s, 2H), 4.70–4.77 (m, 1H), 5.39–5.41 (m, 1H), 6.41 (s, 1H), 7.26–7.40 (m, 5H), 8.13 (s, 1H), 8.17 (s, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 47.1, 61.9 (d, *J* = 8.1 Hz), 63.7, 73.0, 78.9 (t, *J* = 24.9 Hz), 119.5, 122.4, 124.8, 127.3, 128.4, 128.5, 129.0, 134.2–134.4 (m), 138.3, 138.9 (dd, *J* = 19.7, 27.1 Hz), 141.2, 149.9, 153.3, 157.2; ¹⁹F NMR (CDCl₃, 376 MHz), δ -105.7 (d, *J* = 252.3 Hz, 1F), -111.3 (d, *J* = 252.3 Hz, 1F); MS (ESI⁺): Calculated: 374.1429 for C₁₈H₁₈F₂N₅O₂ (M + H)⁺, Found: 374.1430.

General procedure for debenzoylation and depivaloylation

Debenzoylation. Boron tribromide (3 equiv.) (1 M solution in methylene chloride) was added dropwise to a stirred solution of protected nucleoside **28**, **29**, or **31** (1 equiv.) in methylene chloride (15 mL) at -78 °C under a N₂ atmosphere and the mixture was stirred at the same temperature for an additional 2 h. The reaction mixture was quenched with MeOH and neutralized with pyridine. After removal of the solvent under reduced pressure, the reaction mixture was further diluted with water and extracted with methylene chloride twice. The

combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. The crude residue obtained was purified by flash silica gel column chromatography (CH_2Cl_2 :MeOH = 19:1) to yield debenzylated derivatives.

Depivaloylation. A solution of debenzylated derivatives (1 equiv.) in saturated NH_3 /MeOH (5 mL) was stirred at 40 °C for 18 h. The reaction mixture was concentrated under reduced pressure and the crude residue was purified by flash silica gel column chromatography (CH_2Cl_2 :MeOH = 9:1) to yield **8a**, **9a**, or **10**.

(1R,4S,5R)-4-(6-Amino-9H-purin-9-yl)-3,5-difluoro-2-hydroxymethylcyclopent-2-en-ol (8a). White solid. Yield: 65% (for 2 steps); m.p.: 192–194 °C; UV (MeOH) λ_{max} 259 nm; MS (ESI^+): Calculated: 284.0959 for $\text{C}_{11}\text{H}_{12}\text{F}_2\text{N}_5\text{O}_2$ ($\text{M} + \text{H}^+$), Found: 284.0958; $[\alpha]_{\text{D}}^{25} = -60.58$ (c 0.17, MeOH); ^1H NMR (CDCl_3 , 400 MHz) δ 4.18–4.22 (m, 1H), 4.48 (d, $J = 13.2$ Hz, 1H), 5.01–5.17 (m, 2H), 6.02–6.06 (m, 1H), 8.08 (s, 1H), 8.23 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 53.9, 56.8 (dd, $J = 18.3, 21.2$ Hz), 76.3 (dd, $J_{\text{C-F}} = 7.3, 27.8$ Hz), 94.5 (dd, $J_{\text{C-F}} = 5.1, 196.3$ Hz), 120.0, 124.3, 141.5, 141.6, 151.3, 151.6 (d, $J_{\text{C-F}} = 282.7$ Hz), 153.8, 154.2, 157.5; ^{19}F NMR (376 MHz, CDCl_3) δ -127.5, -192.6.

(1R,4S,5R)-4-(6-Amino-9H-purin-9-yl)-5-azido-3-fluoro-2-(hydroxymethyl)cyclopent-2-enol (9a). White solid. Yield: 66% (for 2 steps); m.p.: 180–182 °C; UV (MeOH) λ_{max} 260 nm; MS (ESI^+): Calculated: 307.1067 for $\text{C}_{11}\text{H}_{12}\text{FN}_8\text{O}_2$ ($\text{M} + \text{H}^+$), Found: 307.1067; $[\alpha]_{\text{D}}^{25} = -175.5$ (c 0.2, MeOH); IR (KBr) 2114.9 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz) δ 4.19 (d, $J = 13.2$ Hz, 1H), 4.32 (dd, $J = 4.4, 7.2$ Hz, 1H), 4.50 (d, $J = 13.2$ Hz, 1H), 4.94–4.96 (m, 1H), 5.90 (d, $J = 7.6$ Hz, 1H), 8.06 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 53.8, 57.4 (d, $J = 21.7$ Hz), 68.5 (d, $J = 6.2$ Hz), 77.1 (d, $J = 6.9$ Hz), 120.1, 125.6, 141.2, 151.2 (d, $J_{\text{C-F}} = 282.7$ Hz), 151.4, 154.2, 157.5; ^{19}F NMR (376 MHz, CD_3OD) δ -131.0.

(1R,5S)-5-(6-Amino-9H-purin-9-yl)-4,4-difluoro-3-(hydroxymethyl)cyclopent-2-enol (10). White solid. Yield: 50% (for 2 steps); m.p.: 230–232 °C; UV (MeOH) λ_{max} 260 nm; MS (ESI^+): Calculated: 284.0959 for $\text{C}_{11}\text{H}_{12}\text{F}_2\text{N}_5\text{O}_2$ ($\text{M} + \text{H}^+$), Found: 284.0979; $[\alpha]_{\text{D}}^{25} = +52.3$ (c 1.75, MeOH); ^1H NMR (CD_3OD , 400 MHz) δ 4.31–4.42 (m, 2H), 4.67–4.74 (m, 1H), 5.37–5.40 (m, 1H), 6.33 (s, 1H), 8.14 (s, 1H), 8.19 (s, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 57.8, 63.7 (m), 80.9 (t, $J = 25.4$ Hz), 121.4, 123.8, 126.3, 128.8, 132.7–132.9 (m), 142.4, 144.7, 151.8, 154.8, 158.31; ^{19}F NMR (CDCl_3 , 376 MHz), δ -106.3 (d, $J = 248.1$ Hz, 1F), -112.7 (d, $J = 252.0$ Hz, 1F).

(1R,4S,5R)-5-Amino-4-(6-amino-9H-purin-9-yl)-3-fluoro-2-(hydroxymethyl)cyclopent-2-enol (9b). To a solution of **9a** (0.05 g, 0.15 mmol) in THF (4 mL) was added triphenylphosphine (0.3 mmol) at 0 °C. To this solution, ammonium hydroxide (0.5 mL) and water (0.1 mL) were added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was purified by reverse phase column chromatography ($\text{CH}_3\text{CN}:\text{H}_2\text{O} = 9:1$) to give **9b** (0.04 g, 80%) as a white solid; m.p.: 135–137 °C; UV (MeOH) λ_{max} 260 nm; MS (ESI^+): Calcu-

lated: 281.1162 for $\text{C}_{11}\text{H}_{14}\text{FN}_6\text{O}_2$ ($\text{M} + \text{H}^+$), Found: 281.1161; $[\alpha]_{\text{D}}^{25} = -34.0$ (c 0.45, MeOH); ^1H NMR (CD_3OD , 400 MHz) δ 3.6 (m, 1H), 4.17 d, $J = 13.2$ Hz, 1H), 4.41 (d, $J = 12.8$ Hz, 1H), 4.77 (s, 1H), 5.66 (d, $J = 7.6$ Hz, 1H), 8.05 (s, 1H), 8.21 (s, 1H); ^{13}C NMR (CD_3OD , 100 MHz) δ 51.9, 57.3 (d, $J = 17.3$ Hz), 59.5 (d, $J = 4.3$ Hz), 77.7 (d, $J = 6.7$ Hz), 118.7, 124.5, 140.1, 148.7, 150.1, 151.6, 152.3, 155.6; ^{19}F NMR (376 MHz, CD_3OD) δ -132.2.

General procedure for the synthesis of 32–35

The glycosyl donors **23** and **27** were converted to the pyrimidine nucleosides **32–35** using the Mitsunobu condensation and debenzoylation described earlier.

(1R,4S,5R)-4-(2,4-Dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3,5-difluoro-2-(hydroxymethyl)cyclopent-2-enyl pivalate (32). Yellow foam. Yield: 65%; UV (MeOH) λ_{max} 261 nm; MS (ESI^+): Calculated: 345.1262 for $\text{C}_{15}\text{H}_{19}\text{F}_2\text{N}_2\text{O}_5$ ($\text{M} + \text{H}^+$), Found: 345.1257; $[\alpha]_{\text{D}}^{25} = -113$ (c 0.2, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 1.25 (s, 9H), 2.90 (s, 1H), 3.96 (d, $J = 16.0$ Hz, 1H), 4.48 (d, $J = 14.0$ Hz, 1H), 5.15 (d, $J_{\text{H-F}} = 49.6$ Hz, 1H), 5.80–5.86 (m, 2H), 6.03 (s, 1H), 7.09–7.12 (m, 1H), 9.31 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 27.3, 39.2, 53.7, 57.1 (t, $J = 18.3$ Hz), 77.1, 89.7 (dd, $J_{\text{C-F}} = 5.1, 194.2$ Hz), 102.9, 121.4, 141.5, 151.3, 152.3 (d, $J_{\text{C-F}} = 286.3$ Hz), 163.0, 179.3; ^{19}F NMR (376 MHz, CDCl_3) δ -127.9, -198.7.

(1R,4S,5R)-3,5-Difluoro-2-(hydroxymethyl)-4-(5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)cyclopent-2-enyl pivalate (33). Yellow foam. Yield: 66%; UV (MeOH) λ_{max} 265 nm; MS (ESI^+): Calculated: 359.1419 for $\text{C}_{16}\text{H}_{21}\text{F}_2\text{N}_2\text{O}_5$ ($\text{M} + \text{H}^+$), Found: 359.1414; $[\alpha]_{\text{D}}^{25} = -163.5$ (c 0.2, CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 1.25 (s, 9H), 1.94 (s, 3H), 3.01 (s, 1H), 3.94–3.98 (m, 1H), 4.50 (d, $J = 14.0$ Hz, 1H), 5.14 (d, $J_{\text{H-F}} = 50.0$ Hz, 1H), 5.83 (dd, $J = 5.6, 18.4$ Hz, 1H), 6.01 (s, 1H), 6.90 (s, 1H), 9.38 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 12.6, 27.3, 39.2, 53.7, 56.8 (m), 77.0, 89.7 (dd, $J_{\text{C-F}} = 5.1, 193.7$ Hz), 111.4, 121.0, 137.2, 151.5, 152.4, 152.8 (d, $J_{\text{C-F}} = 286.9$ Hz), 163.8, 179.3; ^{19}F NMR (376 MHz, CDCl_3) δ -127.6, -198.8.

(1R,4S,5R)-5-Azido-4-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-3-fluoro-2-(hydroxymethyl)cyclopent-2-enyl pivalate (34). Yellow foam. Yield: 64%; UV (MeOH) λ_{max} 260 nm; MS (ESI^+): Calculated: 368.1370 for $\text{C}_{15}\text{H}_{19}\text{FN}_5\text{O}_5$ ($\text{M} + \text{H}^+$), Found: 368.1364; $[\alpha]_{\text{D}}^{25} = -40.62$ (c 1.6, CH_2Cl_2); IR (KBr) 2120.1 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz) δ 1.21 (s, 9H), 3.97 (dt, $J = 2.0, 13.2$ Hz, 1H), 4.25 (dt, $J = 2.4, 7.2$ Hz, 1H), 4.37–4.41 (m, 1H), 5.71 (m, 2H), 5.90 (s, 1H), 7.21 (dd, $J = 1.6, 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 27.3, 39.5, 53.4, 58.4, 78.8, 102.7, 122.5, 142.4, 152.3, 152.7 (d, $J_{\text{C-F}} = 284.1$ Hz), 164.9, 179.0; ^{19}F NMR (376 MHz, CDCl_3) δ -123.2.

(1R,4S,5R)-5-Azido-3-fluoro-2-(hydroxymethyl)-4-(5-methyl-2,4-dioxo-3,4-dihydro-pyrimidin-1(2H)-yl)cyclopent-2-enyl pivalate (35). Yellow foam. Yield: 52%; UV (MeOH) λ_{max} 265 nm; MS (ESI^+): Calculated: 382.1527 for $\text{C}_{16}\text{H}_{21}\text{FN}_5\text{O}_5$ ($\text{M} + \text{H}^+$), Found: 382.1522; $[\alpha]_{\text{D}}^{25} = -93.6$ (c 1.75, MeOH); IR (KBr) 2115.6 cm^{-1} ; ^1H NMR (CD_3OD , 400 MHz) δ 1.25 (s, 9H), 1.95 (s, 3H), 3.98 (d, $J = 13.6$ Hz, 1H), 4.37 (d, $J = 7.6$ Hz, 1H), 4.36–4.50 (m, 2H), 5.70 (s, 1H), 5.99 (s, 1H), 6.86 (s, 1H), 9.7 (s, 1H); ^{13}C NMR

(CDCl₃, 100 MHz) δ 12.5, 27.0, 39.0, 53.3, 56.9, 62.6, 78.3 (d, $J = 7.8$ Hz), 111.4, 121.6, 136.3, 151.6, 152.2 (d, $J_{C-F} = 287.3$ Hz), 163.8, 179.20; ¹⁹F NMR (376 MHz, CDCl₃) δ -122.4.

General procedure for the synthesis of 8b, 8c, 9c, and 9d

The pivaloyl derivatives 32–35 were converted to **8b**, **8c**, **9c**, and **9d**, respectively, using the same procedure (NH₃/MeOH, 40 °C, 15 h) described earlier.

1-((1S,4R,5R)-2,5-Difluoro-4-hydroxy-3-(hydroxymethyl)cyclopent-2-enyl)pyrimidine-2,4(1H,3H)-dione (8b). White solid. Yield: 73%; m.p.: 182–184 °C; UV (MeOH) λ_{\max} 261 nm; MS (ESI⁺): Calculated: 261.0687 for C₁₀H₁₁F₂N₂O₄ (M + H)⁺, Found: 261.0683; [α]_D²⁵ = -16.2 (c 1.2, MeOH); ¹H NMR (CD₃OD, 400 MHz) δ 1.89 (s, 3H), 4.14 (dt, $J = 2.4, 12.8$ Hz, 1H), 4.43 (d, $J = 13.2$ Hz, 1H), 4.83–5.02 (m, 2H), 5.70 (d, $J = 8.0$ Hz, 1H), 5.90–5.91 (m, 1H), 7.38–7.41 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 53.8, 58.5 (t, $J = 18.0$ Hz), 75.9–76.3 (m), 94.2 (dd, $J_{C-F} = 5.6, 193.7$ Hz), 102.6, 125.2, 144.0, 151.6 (d, $J_{C-F} = 282.2$ Hz), 152.9, 166.0; ¹⁹F NMR (376 MHz, CDCl₃) δ -131.6, -196.6.

1-((1S,4R,5R)-2,5-Difluoro-4-hydroxy-3-(hydroxymethyl)cyclopent-2-enyl)-5-methyl-pyrimidine-2,4(1H,3H)-dione (8c). White solid. Yield: 66%; m.p.: 181–183 °C; UV (MeOH) λ_{\max} 265 nm; MS (ESI⁺): Calculated: 275.0843 for C₁₁H₁₃F₂N₂O₄ (M + H)⁺, Found: 275.0839; [α]_D²⁵ = -39 (c 0.2, MeOH); ¹H NMR (CD₃OD, 400 MHz) δ 1.88 (s, 3H), 3.02–3.32 (m, 1H), 4.14 (dt, $J = 2.4, 10.8$ Hz, 1H), 4.44 (d, $J = 13.2$ Hz, 1H), 4.85–5.02 (m, 2H), 5.49 (s, 1H), 5.89 (s, 1H), 7.21 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ 12.2, 53.7, 58.2 (t, 18.3 Hz), 76.2 (dd, $J = 7.7, 28.3$ Hz), 94.3 (dd, $J_{C-F} = 6.1, 194.5$ Hz), 111.5, 124.8, 139.4, 152.0 (d, $J_{C-F} = 282.0$ Hz), 153.1, 166.3; ¹⁹F NMR (376 MHz, CDCl₃) δ -131.4, -195.9.

1-((1S,4R,5R)-5-Azido-2-fluoro-4-hydroxy-3-(hydroxymethyl)cyclopent-2-enyl)pyrimidine-2,4(1H,3H)-dione (9c). White solid. Yield: 50%; m.p.: 170–172 °C; UV (MeOH) λ_{\max} 262 nm; MS (ESI⁺): Calculated: 306.0615 for C₁₀H₁₀FN₃NaO₄ (M + Na)⁺, Found: 306.0614; [α]_D²⁵ = -62.3 (c 1.3, MeOH); IR (KBr) 2117 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) δ 4.11–4.14 (m, 1H), 4.21–4.24 (m, 1H), 4.40 (d, $J = 13.2$ Hz, 1H), 4.73 (s, 1H), 5.74 (d, $J = 8.0$ Hz, 1H), 5.85 (s, 1H), 7.14 (s, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 53.7, 58.8, 64.4, 67.8, 77.1 (d, $J = 7.0$ Hz), 102.9, 126.5, 143.1, 151.4 (d, $J_{C-F} = 281.8$ Hz), 153.1, 166.0; ¹⁹F NMR (376 MHz, CD₃OD) δ -130.44.

1-((1S,4R,5R)-5-Azido-2-fluoro-4-hydroxy-3-(hydroxymethyl)cyclopent-2-enyl)-5-methylpyrimidine-2,4(1H,3H)-dione (9d). White solid. Yield: 75%; m.p.: 172–174 °C; UV (MeOH) λ_{\max} 265 nm; MS (ESI⁺): Calculated: 298.0952 for C₁₁H₁₃FN₃O₄ (M + H)⁺, Found: 298.0948; [α]_D²⁵ = -88.5 (c 1.75, MeOH); IR (KBr) 2112.7 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) δ 1.90 (s, 3H), 4.10–4.22 (m, 2H), 4.37 (d, $J = 12.8$ Hz, 1H), 4.74 (s, 1H), 5.85 (s, 1H), 7.14 (s, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 12.3, 53.6, 58.6, 67.83, 77.0 (d, $J = 4.7$ Hz), 112.0, 126.2, 138.3, 151.4 (d, $J_{C-F} = 282.5$ Hz), 153.3, 166.3; ¹⁹F NMR (376 MHz, CD₃OD) δ -130.2.

4-Amino-1-((1S,4R,5R)-2,5-difluoro-4-hydroxy-3-(hydroxymethyl)cyclopent-2-enyl)pyrimidin-2(1H)-one (8d). To a stirred suspension of **32** (0.3 g, 0.87 mmol) in methylene chloride

(10 mL) were added pyridine (0.35 mL, 4.35 mmol) and acetic anhydride (0.25 mL, 2.62 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with methylene chloride (15 mL). The organic layer was washed with brine, dried over anhydrous MgSO₄, filtered, and evaporated. The residue was purified by short silica gel column chromatography (hexane:EtOAc = 4:1) to give acetyl derivative as a yellow syrup (0.27 g, 81%).

An ice cold solution of 1,2,4-triazole (0.49 g, 7.12 mmol) in anhydrous acetonitrile (5 mL) was treated with phosphorus oxychloride (0.66 mL, 7.12 mmol) at 0 °C under a N₂ atmosphere and the mixture was stirred at the same temperature for 30 min. To this solution, acetylated derivative (0.27 g, 0.71 mmol) in acetonitrile (5 mL) and triethylamine (0.99 mL, 7.12 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was evaporated and the orange residue obtained was redissolved in methylene chloride (20 mL) and extracted with water (10 mL). The organic layer was washed with brine, dried over anhydrous MgSO₄, filtered and evaporated. The residue obtained was dissolved in solution of NH₄OH (3 mL) in 1,4-dioxane (5 mL) and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash silica gel column chromatography to yield **36**, which was converted to target derivative **8d** as a white solid, using the same procedure used for the synthesis of **8b**, **8c**, **9c**, and **9d**. Yield: 71% (3 steps); m.p.: 207–208 °C; UV (MeOH) λ_{\max} 271 nm; MS (ESI⁺): Calculated: 260.0847 for C₁₀H₁₂F₂N₃O₃ (M + H)⁺, Found: 260.0843; [α]_D²⁵ = -18 (c 0.2, MeOH); ¹H NMR (CD₃OD, 400 MHz) δ 4.14 (dt, $J = 2.4, 13.2$ Hz, 1H), 4.43 (d, $J = 12.8$ Hz, 1H), 4.80–5.03 (m, 2H), 5.89 (d, $J = 7.6$ Hz, 1H), 6.0 (s, 1H), 7.37 (dt, $J = 1.6, 7.6$ Hz, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 53.7, 59.4 (t, $J = 18.3$ Hz), 76.1 (dd, $J = 7.4, 28.6$ Hz), 94.1 (dd, $J_{C-F} = 5.9, 194.1$ Hz), 96.0, 124.7, 144.4, 152.6 (d, $J_{C-F} = 282.7$ Hz), 159.0, 167.8; ¹⁹F NMR (376 MHz, CDCl₃) δ -131.5, -196.2.

4-Amino-1-((1S,4R,5R)-5-azido-2-fluoro-4-hydroxy-3-(hydroxymethyl)cyclopent-2-enyl)pyrimidin-2(1H)-one (9e). Compound **34** was converted to **9e** according to the same procedure used in the synthesis of **8d**: white solid; yield: 66% (3 steps); m.p.: 173–175 °C; UV (MeOH) λ_{\max} 273 nm; MS (ESI⁺): Calculated: 283.0955 for C₁₀H₁₂FN₃O₃ (M + H)⁺, Found: 283.0952; [α]_D²⁵ = -34.1 (c 0.44, MeOH); IR (KBr) 2115.8 cm⁻¹; ¹H NMR (CD₃OD, 400 MHz) δ 4.12 (dt, $J = 1.6, 13.6$ Hz, 1H), 4.20–4.22 (m, 1H), 4.40 (d, $J = 13.2$ Hz, 1H), 4.69 (s, 1H), 5.92 (d, $J = 7.6$ Hz, 1H), 5.96 (s, 1H), 7.33 (dd, $J = 2.0, 7.6$ Hz, 1H); ¹³C NMR (CD₃OD, 100 MHz) δ 53.7, 59.7, 68.0, 77.0 (d, $J = 6.1$ Hz), 96.3, 125.9, 143.6, 152.1 (d, $J_{C-F} = 282.5$ Hz), 159.1, 167.7; ¹⁹F NMR (376 MHz, CD₃OD) δ -130.2.

Acknowledgements

This work was supported by the grant from Mid-career Research Program (370C-20130120) of National Research Foundation (NRF) of Korea.

References

- 1 R. S. Hosmane, in *Kirk-Othmer Concise Encyclopedia of Chemical Technology*, ed. Kirk-Othmer, John-Wiley and Sons, Inc., Hoboken, NJ, USA, 5th edn, 2007, vol. 2, pp. 132–182.
- 2 (a) *Antiviral Nucleosides: Chiral Synthesis and Chemotherapy*, ed. C. K. Chu, Elsevier B. V., Amsterdam, The Netherlands, 2003; (b) *Modified Nucleosides: in Biochemistry, Biotechnology and Medicine*, ed. P. Herdewijn, Wiley-VCH, Weinheim, Germany, 2008; (c) D. K. Tosh, K. A. Jacobson and L. S. Jeong, *Drugs Future*, 2009, **34**, 43–52.
- 3 (a) L. S. Jeong and J. A. Lee, *Antiviral Chem. Chemother.*, 2004, **5**, 235–250; (b) O. Boutureira, M. I. Matheu, Y. Diaz and S. Castillon, *Chem. Soc. Rev.*, 2013, **42**, 5056–5072; (c) V. A. Mulamootil, A. Nayak and L. S. Jeong, *Asian J. Org. Chem.*, 2014, **3**, 748–761.
- 4 (a) E. S. Matyugina, A. L. Khandazhinskaya and S. N. Kochetkov, *Russ. Chem. Rev.*, 2012, **81**, 729–746; (b) J. Wang, R. K. Rawal and C. K. Chu, in *Medicinal Chemistry of Nucleic Acids*, ed. L. H. Zhang, Z. Xi and J. Chattopadhyaya, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2011, DOI: 10.1002/9781118092804.ch1.
- 5 (a) *Nucleoside Mimetics: Their Chemistry and Biological Properties*, ed. C. Simons, Gordon and Breach Science Publishers, Amsterdam, 2001; (b) S. W. Schneller, *Curr. Top. Med. Chem.*, 2002, **2**, 1087–1092.
- 6 (a) E. De Clercq, *Antimicrob. Agents Chemother.*, 1985, **28**, 84–89; (b) M. Inaba, K. Nagashima, S. Tsukagoshi and Y. Sakurai, *Cancer Res.*, 1986, **46**, 1063–1067.
- 7 L. L. Bennett, Jr., P. W. Allan, L. M. Rose, R. N. Comber and J. A. Secrist, *Mol. Pharmacol.*, 1986, **29**, 383–390.
- 8 N. A. Meanwell, S. V. D'Andrea, C. W. Cianci, I. B. Dicker, K. S. Yeung, M. Belema and M. Krystal, in *Drug Discovery: Practices, Processes, and Perspectives*, ed. J. J. Li and E. J. Corey, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2013, pp. 439–515.
- 9 J. M. Huraux, D. Ingrand and H. Agut, *Fundam. Clin. Pharmacol.*, 1990, **4**, 357–481.
- 10 E. De Clercq and P. Herdewijn, in *Pharmaceutical Sciences Encyclopedia*, ed. S. C. Gad, John Wiley & Sons, Inc., Hoboken, NJ, USA, 2010, pp. 1–56.
- 11 W. Saenger, *Angew. Chem., Int. Ed. Engl.*, 1973, **12**, 591–601.
- 12 (a) E. De Clercq and M. Cools, *Biochem. Biophys. Res. Commun.*, 1985, **129**, 306–311; (b) E. De Clercq, *Nucleosides Nucleotides*, 1998, **17**, 625–634.
- 13 (a) V. E. Marquez, M.-I. Lim, S. P. Treanor, J. Plowman, M. A. Priest, A. Markovac, M. S. Khan, B. Kaskar and J. S. Driscoll, *J. Med. Chem.*, 1988, **31**, 1687–1694; (b) E. De Clercq, J. Murase and V. E. Marquez, *Biochem. Pharmacol.*, 1991, **41**, 1821–1829.
- 14 (a) L. S. Jeong, S. J. Yoo, K. M. Lee, M. J. Koo, W. J. Choi, H. O. Kim, H. R. Moon, M. Y. Lee, J. G. Park, S. K. Lee and M. W. Chun, *J. Med. Chem.*, 2003, **46**, 201–203; (b) K. M. Lee, W. J. Choi, Y. Lee, H. J. Lee, L. X. Zhao, H. W. Lee, J. G. Park, H. O. Kim, K. Y. Hwang, Y.-S. Heo, S. Choi and L. S. Jeong, *J. Med. Chem.*, 2011, **54**, 930–938.
- 15 W. J. Choi, H.-J. Chung, G. Chandra, V. Alexander, L. X. Zhao, H. W. Lee, A. Nayak, M. S. Majik, H. O. Kim, J. H. Kim, Y. B. Lee, C. H. Ahn, S. K. Lee and L. S. Jeong, *J. Med. Chem.*, 2012, **55**, 4521–4525.
- 16 G. J. Peters, K. Smid, L. Vechhi, I. Kathmann, D. Sarkisjan, R. J. Honeywell, N. Losekoot, O. Ohne, A. Orbach, E. Blaugrund, L. S. Jeong, Y. B. Lee, C. H. Ahn and D. J. Kim, *Invest. New Drugs*, 2013, **31**, 1444–1457.
- 17 (a) X. L. Qiu, X. H. Xu and F. L. Qing, *Tetrahedron*, 2010, **66**, 789–843; (b) K. W. Pankiewicz, *Carbohydr. Res.*, 2000, **327**, 87–105; (c) H. W. Rajchel, *J. Fluorine Chem.*, 2012, **143**, 11–48.
- 18 K. A. Watanabe, U. Reichman, K. Hirota, C. Lopez and J. J. Fox, *J. Med. Chem.*, 1979, **22**, 21–24.
- 19 T. Pathak, *Chem. Rev.*, 2002, **102**, 1623–1668.
- 20 (a) S. Rodriguez, D. Edmont, C. Mathé and C. Périgaud, *Tetrahedron*, 2007, 7165–7171; (b) M. J. Comin, S. C. Pellegrinet and J. B. Rodriguez, *ARKIVOC*, 2005, **xii**, 205–213.
- 21 W. J. Choi, H. R. Moon, H. O. Kim, B. N. Yoo, J. A. Lee, D. H. Shin and L. S. Jeong, *J. Org. Chem.*, 2004, **69**, 2634–2636.
- 22 S. K. Lee, Y. H. Heo, V. E. Steele and J. M. Pezzuto, *Anticancer Res.*, 2002, **22**, 97–102.
- 23 (a) H. R. Moon, K. M. Lee, H. J. Lee, S. K. Lee, S. B. Park, M. W. Chun and L. S. Jeong, *Nucleosides, Nucleotides Nucleic Acids*, 2005, **24**, 707–708; (b) H. R. Moon, H. J. Lee, K. R. Kim, K. M. Lee, S. K. Lee, H. O. Kim, M. W. Chun and L. S. Jeong, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 5641–5644.