Tetrahedron 67 (2011) 3388–3394

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides via Reformatskii–Claisen rearrangement

Yi Yang [a], Feng Zheng [a], Feng-Ling Qing [a,b,*]

[a] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China
[b] College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, 2999 North Renmin Lu, Shanghai 201620, China

ARTICLE INFO

Article history:
Received 26 January 2011
Received in revised form 8 March 2011
Accepted 17 March 2011
Available online 25 March 2011

Keywords:
Fluorinated carbocyclic nucleosides
Reformatskii–Claisen rearrangement
Ring-closing metathesis
Mitsunobu reaction

ABSTRACT

2′,3′-Dideoxy-6′-fluorocarbocyclic nucleosides, analogues of highly bioactive carbovir and abacavir were synthesized. The notable steps were the incorporation of fluoromethylene group by way of silicon-induced Reformatskii–Claisen rearrangement of allyl bromofluoroacetate, the construction of the carbocyclic ring via ring-closing metathesis (RCM) and the introduction of base by Mitsunobu reaction.

1. Introduction

Carbocyclic nucleosides (CNAs),[1] in which the oxygen in the sugar portion of the nucleoside was replaced with a methylene (CH_2) unit, are highly resistant to the phosphorylases that cleave the *N*-glycosidic linkage in conventional nucleosides. In recent years, structural modification of carbocyclic nucleosides has attracted much attention in order to find more effective antiviral and antitumor agents. Carbovir[2] and Abacavir[3] are the most representative carbocyclic nucleosides because of their potent and selective inhibition of human immunodeficiency virus (HIV). Furthermore, the position C-6′ at carbocyclic framework may provide a platform for structural elaboration, that is, not available in the common ribofuranosyl based nucleosides. It is well-known that fluorine is often used to replace hydrogen in medicinal chemistry due to its small size and high compactness. Several synthetically derived C-6′ fluorinated carbocyclic nucleosides have been studied.[4] Among these C-6′ fluorinated carbocyclic nucleosides, 6′-fluoroaristeromycin exhibited moderate activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) and served as potent inhibitors of AdoHcy hydrolase in vitro.[4l] During our ongoing search for new antiviral and antitumor agents, we are interested in stereoselective introduction of a fluorine atom at position C-6′ of carbocyclic nucleosides. Herein, we describe rational design and stereoselective synthesis of 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides **1** (Fig. 1). The design of 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides is based on the fact that 2′,3′-dideoxynucleoside (ddNs) is a kind of effective therapeutic agents against HIV and hepatitis B virus (HBV), such as 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T),[5] an anti-HIV drug. In addition, nucleosides **1** are analogues of the highly bioactive Carbovir and Abacavir in which the methylene (CH_2) unite of C-6′ site in sugar moiety was replaced

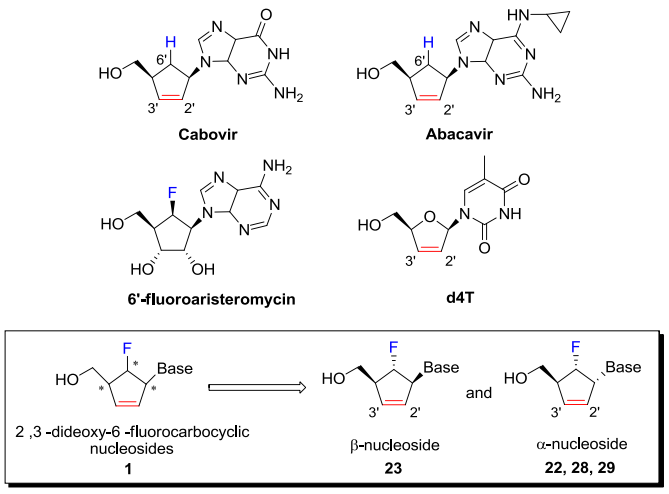


Fig. 1. Rational design of the target molecule **1**.

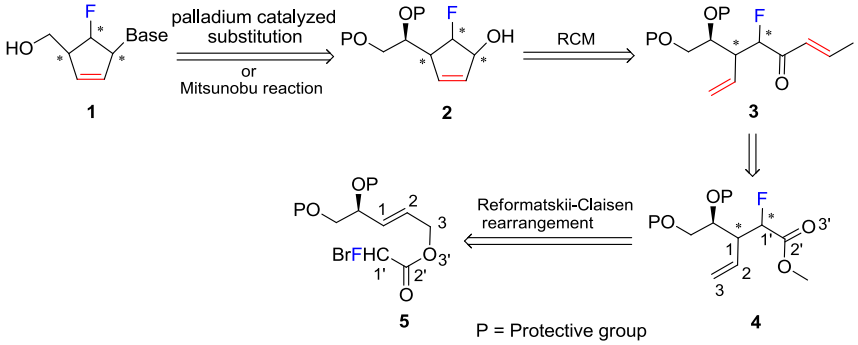
* Corresponding author. Fax: +86 21 64166128; e-mail address: flq@mail.sioc.ac.cn (F.-L. Qing).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.054

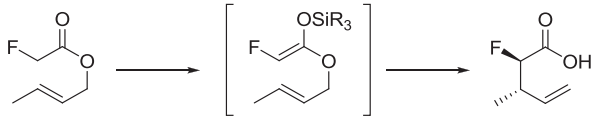
with a fluoromethylene (CHF) group, which may provide us a chance to further study the fluorine effects in the bioactivities of these carbocyclic nucleosides.

2. Results and discussion

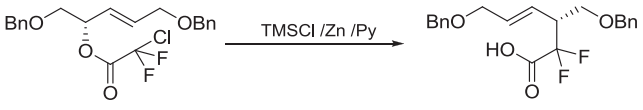
The synthetic strategy was based on that the target molecule **1** could be derived from the precursor **2** by introduction of a base moiety via palladium-catalyzed allylic substitution[6,11b] or Mitsunobu reaction[7] (Scheme 1). The ring-closing metathesis[8] of diene **3** would provide carbocyclic sugar **2**. Compound **3** could be easily prepared from the key intermediate **4**, which can be prepared via the Reformatskii–Claisen reaction of allyl α-bromofluoroacetate **5**. Although Welch and co-workers had reported the stereoselective rearrangement of allyl α-fluoro-acetates via α-fluoro silyl ketene acetal (Scheme 2),[9] the starting material fluoroacetic acid (FCH_2CO_2H) for preparation of allyl α-fluoroacetates is very toxic.[10a,b] Inspired by our recent work relating the silicon-induced stereoselective Reformatskii–Claisen rearrangement of secondary allyl chlorodifluoroacetate (Scheme 3),[11] we expected that the construction of **4** from the much less poisonous bromofluoroacetic acid[10c,d] would be feasible and safe.



Scheme 1. Retrosynthesis of compound **1**.



Scheme 2.



Scheme 3.

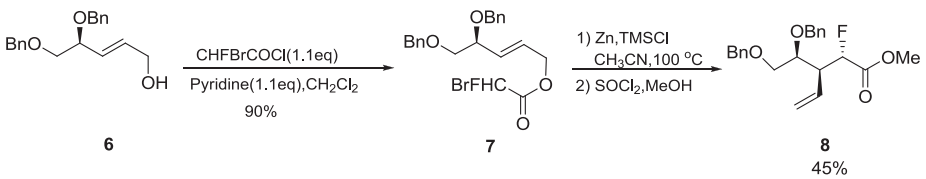
Accordingly, the synthesis of target molecules began by preparation of allyl bromofluoroacetate **7**. Treatment of allylic alcohol **6**[11b] with bromofluoroacetyl chloride in the presence of pyridine afforded ester **7** in 90% yield (Scheme 4). Then the silicon-induced Reformatskii–Claisen reaction of compound **7** (a mixture of **7**, 2.0 equiv of TMSCl and 10.0 equiv of fresh activated zinc was stirred in dry acetonitrile at 100 °C for 12 h), followed by esterification with $SOCl_2$/MeOH provided the monofluorinated esters in 70% overall yield with four diastereoisomers (8.7:3.4:1.8:1, determined by ^{19}F NMR). Fortunately, the major diastereoisomer **8** could be separated by flash chromatography in 45% yield (Scheme 4).

With the key ester **8** in hand, we then turned our attention to establish the carbocyclic sugar (Scheme 5). Ester **8** was transformed to Weinreb amide **9** in 87% yield. Allylation of **9** with allylmagnesium chloride at −78 °C, followed by triethylamine-induced double bond isomerization gave the α,β-unsaturated ketone **10** in 94% yield. Ring-closing metathesis of electron-deficient diene **10** with Grubbs-II catalyst (5 mol %) in toluene at 100 °C proceeded smoothly, providing the desired product **11** in 95% yield. Luche reduction of compound **11** afforded alcohols **12** and **13** in a ratio of 3.2:1, which were converted to allyl carbonate **14** and **15**, respectively. Unfortunately, attempts to install a base moiety into carbonate **14** and **15** via palladium-catalyzed allylic substitution reaction[11b] failed to give any desired product (Scheme 6).

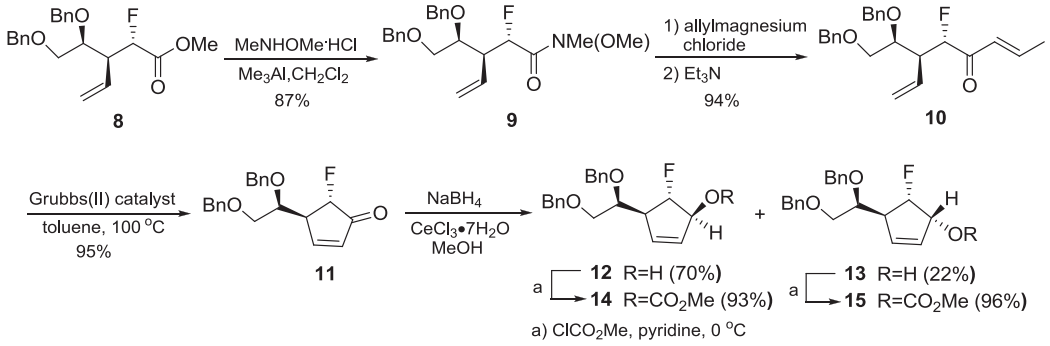
Alternatively, the Mitsunobo reaction was investigated for introduction of bases (Scheme 7). To our delight, the coupling of alcohol **12** with 6-chloropurine in the presence of DEAD and PPh_3 afforded compound **16** in moderate yield. Amination of compound **16** with NH_3/CH_3OH at 80 °C afforded compound **18** in good yield. Deprotection of benzyl group with BCl_3, followed by oxidation of the resulting vicinal diol **20** with $NaIO_4$ and subsequent reduction of aldehyde with $NaBH_4$ successfully afforded α-nucleoside **22**. Using same strategy, fluorinated β-nucleoside **23** was also obtained from alcohol **13**.

Encouraged by the successful access to nucleosides **22** and **23**, α-uridine **28** and α-thymidine **29** were also obtained in a similar way (Scheme 8).

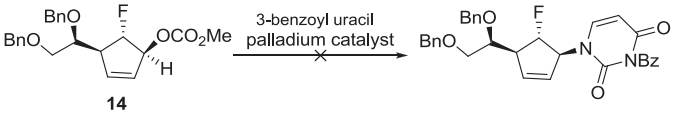
The stereochemistry assignments of final products were established by 2D NMR NOESY experiment of compound **12** and the X-ray crystal analysis[12] of compound **18** (Fig. 2).



Scheme 4. Reformatskii–Claisen rearrangement of compound **7**.

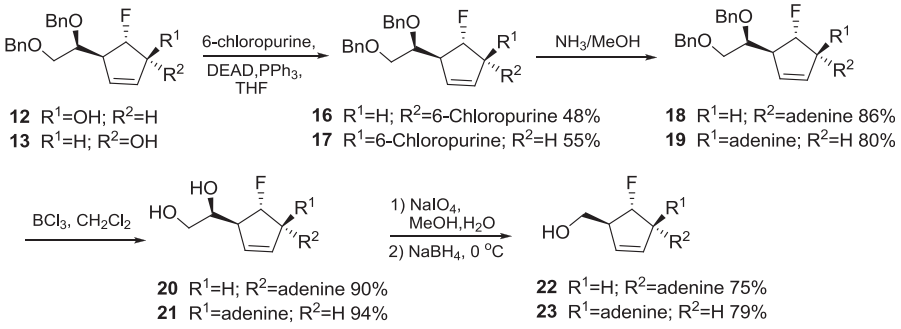


Scheme 5.

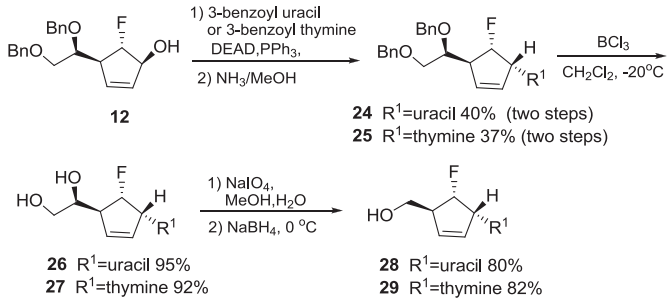


Scheme 6.

highlighted the preparation of chiral fluorinated building block **8** via silicon-induced Reformatskii–Claisen rearrangement of allyl bromofluoroacetate, construction of the carbocyclic ring through RCM, and installation of the base moiety by Mitsunobu reaction.



Scheme 7.



Scheme 8.

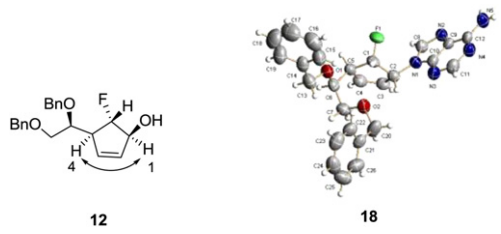


Fig. 2. NOESY correlation of compound **12** and X-ray structure of compound **18**.

3. Conclusion

We described herein the design and synthesis of 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides **22**, **23**, **28**, and **29**. Our synthesis

4. Experimental section

4.1. General

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. THF was distilled from sodium and benzophenone. Dichloromethane was distilled from calcium hydride. Petroleum ether refers to the fraction of light petroleum ether with bp 60–90 °C ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AM-300, Bruker AM-400 or Varian Mercury-300 spectrometers. ^{19}F NMR was recorded on a Bruker AM-300 spectrometer ($FCCl_3$ as outside standard and low field is positive). Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are in hertz. Optical rotations were measured using a Perkin–Elmer 241 or 341 polarimeter. Crystallographic data were analyzed with Rigaku FCR Diffractimer.

4.2. Synthesis and characterization

*4.2.1. (S,E)-4,5-Bis(benzyloxy)pent-2-enyl 2-bromo-2-fluoroacetate (**7**).* To a solution of compound **6** (150 mg, 0.50 mmol) in anhydrous dichloromethane (3 mL) was added pyridine (48 μL, 0.60 mmol) dropwise at 0 °C. After the reaction mixture was stirred for 5 min at 0 °C, bromofluoroacetyl chloride (81 μL, 0.60 mmol) was added dropwise. After stirring for 1 h at 0 °C, the reaction mixture was then warmed to ambient temperature and stirred for 12 h. Dichloromethane (5 mL) was added to the reaction system and the resultant organic phase was washed with saturated copper sulfate solution (5 mL×3) and water (5 mL), dried over anhydrous Na_2SO_4,

filtered, and concentrated. The residue was purified by flash chromatography (petroleum ether/ethyl acetate=15:1) to give compound **7** as a clear oil (196 mg, 90% yield): $[\alpha]_{D^{25}}$ 15.4° (*c* 4.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.21 (m, 10H), 6.56 (d, *J*=50.1 Hz, 1H), 5.86 (m, 2H), 4.77 (d, *J*=4.2 Hz, 2H), 4.65–4.46 (m, 4H), 4.08 (dd, *J*=4.8, 5.2 Hz, 1H), 3.62–3.49 (m, 2H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 164.5 (d, *J*=26.1 Hz), 138.5, 138.4, 134.2, 134.1, 128.7, 128.0, 127.9, 127.9, 126.0, 82.3, 79.7, 78.1, 73.7, 72.9, 71.2, 66.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −150.17 (d, *J*=50.5 Hz, 1F); IR (KBr) ν_{max} 3063, 3030, 2862, 1766, 1091 cm^{-1}; MS (ESI) *m/z* 454 $(M+NH_4)^+$; HRMS calcd for $C_{21}H_{22}FBrO_4$: 436.0685; found: 436.0687.

*4.2.2. (2S,3S)-Methyl 3-((S)-1,2-bis(benzyloxy)ethyl)-2-fluoropent-4-enoate(**8**).* A mixture of compound **7** (211 mg, 0.48 mmol), chlorotrimethyl silane (0.18 mL, 1.04 mmol) and freshly activated zinc dust (420 mg, 6.45 mmol) in dry acetonitrile (3 mL) was heated to 100 °C over a period of 20 min and stirred for 10 h at the same temperature. After the reaction mixture cooled to room temperature, the mixture was filtered and the residue was washed by MeOH (1.5 mL×2). To the combined organic solution, $SOCl_2$ (0.3 mL, 4.14 mmol) was added slowly and then stirred for 3 h. Water (5 mL) was added to quench the reaction and the solvent was partially removed in vacuo. The resultant mixture was extracted with Et_2O (5 mL×3). The combined organic layer was washed with brine, and dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=25:1) to give compound **8** as a colorless oil (70 mg, 45% yield) : $[\alpha]_{D^{25}}$ 10.6° (*c* 2.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.22 (m, 10H), 5.81–5.69 (m, 1H), 5.19–5.05 (m, 2H), 4.91–4.44 (m, 5H), 4.00(s, 1H), 3.61 (s, 2H), 3.63–3.49 (m, 2H), 2.87 (dd, *J*=11.7, 12.0 Hz, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 169.5 (d, *J*=24.0 Hz), 138.4, 138.1, 130.8, 130.7, 128.4, 127.7, 127.6, 127.6, 120.6, 88.8 (d, *J*=187.4 Hz), 76.7, 75.7, 73.4, 73.3, 71.1, 51.9, 49.7, 49.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −191.6 (dd, *J*=34.4, 13.5 Hz 1F); IR (KBr) ν_{max} 3030, 2951, 2862, 1758, 1102, 696 cm^{-1}; MS (ESI) *m/z* 373 $(M+H)^+$, 390 $(M+NH_4)^+$; HRMS calcd for $C_{22}H_{25}FO_4Na$: 395.1635; found: 395.1629.

*4.2.3. (2S,3S)-3-((S)-1,2-Bis(benzyloxy)ethyl)-2-fluoro-N-methoxy-N-methylpent-4-enamide(**9**).* To a stirred suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (300 mg, 3.08 mmol,) in CH_2Cl_2 (10 mL) at 0 °C was slowly added $AlMe_3$ (2.0 M solution in toluene, 1.54 mL, 3.08 mmol). After stirring for 60 min, compound **8** (380 mg, 1.03 mmol) in CH_2Cl_2 (5 mL) was added dropwise at 0 °C. Then the reaction mixture was warmed to room temperature and stirred for 24 h. Saturated NH_4Cl solution (40 mL) was added slowly to quench the reaction (caution: methane will bulb outside). Then HCl solution (0.5 M, 10 mL) was added to dissolve some precipitate. The aqueous phase was extracted with ethyl acetate, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=5:1) to give compound **9** as a clear oil (360 mg, 87% yield) : $[\alpha]_{D^{25}}$ 32.4° (*c* 3.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 10H), 5.82–5.73 (m, 1H), 5.41 (dd, *J*=9.9, 49.8 Hz, 1H), 5.16–5.11 (m, 2H), 4.86(d, *J*=11.4 Hz, 1H), 4.62 (d, *J*=11.4 Hz, 1H), 4.53 (d, *J*=12.6 Hz, 1H), 4.49 (d, *J*=12.6 Hz, 1H), 4.09 (t, *J*=5.1 Hz, 1H), 3.63 (s, 3H), 3.60–3.46 (m, 2H), 3.14 (s, 3H), 2.98 (dd, *J*=19.2, 9.6 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 168.0 (d, *J*=23.9 Hz), 137.9, 137.2, 129.6, 129.5, 127.4, 127.3, 126.6, 126.5, 126.5, 120.0, 84.8 (d, *J*=180.3 Hz), 76.4, 76.0, 75.7, 74.7, 72.7, 72.3, 71.0, 60.6, 48.4, 48.2, 31.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −190.9 (dd, *J*=9.6, 49.6 Hz, 1F); IR (KBr) ν_{max} 3064, 2916, 1686, 1677, 1452, 1106, 698 cm^{-1}; MS(ESI) *m/z* 402 $(M+H)^+$; HRMS calcd for $C_{22}H_{29}FO_7$: 424.1897; found: 424.1892.

*4.2.4. (5S,6S,E)-6-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluoroocta-2,7-dien-4-one(**10**).* To a stirred solution of **9** (200 mg, 0.5 mmol) in THF (5 mL) was added allylmagnesium chloride (1.2 mL, 2.04 mmol, 1.7 M solution in THF) at −78 °C. After being stirred for 60 min at −78 °C, the reaction was quenched with 1 M HCl (10 mL). The aqueous layer was extracted with ether (5 mL×2). The combined organic layer was washed with water and brine, dried over Na_2SO_4. The solvent was removed in vacuo and the residue was dissolved in THF (5 mL). The resulting solution was then treated with Et_3N (0.2 mL) and stirred overnight. The solvent was removed under reduced pressure and then the residue was purified by flash chromatography (petroleum ether/ethyl acetate=20:1) on silica gel to give **10** as a yellow oil (180 mg, 94% yield): $[\alpha]_{D^{25}}$ −15.7° (*c* 3.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.23 (m, 10H), 7.04–6.92 (m, 1H), 6.46–6.41 (m, 1H), 5.75–5.66 (td, *J*=6.1, 7.5 Hz, 1H), 5.17–5.00 (m, 3H), 4.88–4.45 (m, 4H), 4.62 (td, *J*=3.0, 4.5 Hz, 1H), 3.65–3.47 (m, 2H), 2.83 (ddd, *J*=2.1, 9.3, 12.6 Hz, 1H), 1.89 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 195.5 (d, *J*=22.5 Hz), 145.5, 145.5, 138.3, 138.0, 131.0, 130.9, 128.3, 128.2, 127.6, 127.5, 127.5, 126.3, 120.4, 93.6 (d, *J*=188.9 Hz), 76.6, 75.8, 75.7, 73.2, 73.1, 71.0, 49.0 (d, *J*=20.2 Hz), 18.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −191.9 (dd, *J*=11.8, 49.6 Hz, 1F); IR (KBr) ν_{max} 3064, 3030, 2912, 2864, 1699, 1629, 1099 cm^{-1}; MS (ESI) *m/z* 383 $(M+H)^+$; HRMS calcd for $C_{24}H_{27}FO_3Na$: 405.1842; found: 405.1836.

*4.2.5. (4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enone (**11**).* A solution of Grubbs-II catalyst (10 mg) in toluene (5 mL) was added slowly to a solution of compound **10** (150 mg, 0.39 mmol) in toluene (10 ml) at 100 °C and the reaction mixture was heated for 16 h at 100 °C. After removing the solvent in vacuo, the residue was purified by flash chromatography (petroleum ether/ethyl acetate=8:1) on silica gel to give **11** as a yellow oil (120 mg, 95%): $[\alpha]_{D^{25}}$ −140.3° (*c* 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.39–7.25 (m, 10H), 6.21 (d, *J*=5.7 Hz 1H), 4.90–4.51 (m, 5 H), 3.84–3.66 (m, 3H), 3.31–3.22 (m, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 201.0 (d, *J*=15.8 Hz), 160.4, 160.3, 136.6, 136.5, 131.3, 127.6, 127.5, 127.5, 127.4, 127.4, 127.1, 126.9, 126.9, 126.8, 126.7, 89.8 (d, *J*=191.9 Hz), 75.8, 75.3, 72.6, 71.3, 69.0, 48.5 (d, *J*=30.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −198.3 (dd, *J*=51.3, 20.0 Hz, 1F); IR (KBr) ν_{max} 3063, 3030, 2866, 1726, 1583, 1454, 1090, 1028 cm^{-1}; MS (ESI) *m/z* 341 $(M+H)^+$; 358 $(M+NH_4)^+$; HRMS calcd for $C_{21}H_{21}FO_3Na$: 363.1372; found: 363.1367.

*4.2.6. (1S,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enol(12) and (1R,4S,5S)-4-((S)-1,2-bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enol(**13**).* A solution of **11** (204 mg, 0.603 mmol) and $CeCl_3 \cdot 7H_2O$ (1.3 g, 3.49 mmol) in methanol (10 mL) was cooled to 0 °C, and $NaBH_4$ (76 mg, 2 mmol) was added in portions. The solution was remained at 0 °C for 1 h and quenched with aqueous ammonium chloride (20 mL). The mixture was extracted with ethyl acetate (15 mL×3), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate=5:1) on silica gel to give **12** (144 mg, 70%) and **13** as a clear oil (45 mg, 22%).

Data for compound **12**: $[\alpha]_{D^{25}}$ −45.2° (*c* 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.32 (m, 10H), 5.94–5.87 (m, 2H), 4.84 (d, *J*=51.1 Hz, 1H), 4.80–4.57 (m, 5H), 3.89–3.96 (m, 1H), 3.71 (dd, *J*=5.3, 10.2 Hz, 1H), 3.65 (dd, *J*=5.3, 10.2 Hz, 1H), 3.10 (ddd, *J*=2.0, 4.1, 6.1 Hz), 2.73 (d, *J*=9.8 Hz, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 138.0, 137.4, 134.0, 133.9, 131.8, 128.9, 128.8, 128.7, 128.5, 128.2, 128.0, 101.6 (d, *J*=182.0 Hz), 80.4, 80.1, 73.8, 72.9, 70.9, 53.5 (d, *J*=24.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −179.1 (m, 1F); IR (KBr) ν_{max} 3422, 3030, 2862, 1496, 1453,1246, 1095 cm^{-1}; MS(ESI) *m/z* 360 $(M+NH_4)^+$; HRMS calcd for $C_{21}H_{23}FO_3Na$: 365.1529; found: 365.1523.

Data for compound **13**: $[\alpha]_{D^{25}}$ −139.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.56 (m, 10H), 6.20 (s, 2H), 5.13 (d, *J*=60.3 Hz, 1H), 5.03–4.81 (m, 5H), 4.08 (d, *J*=4.8 Hz, 1H), 3.91–3.88 (m, 2H), 3.52 (d, *J*=22.5 Hz, 1H), 2.45 (br, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 138.0, 137.9, 133.5, 131.7, 131.6, 128.4, 128.3, 127.8, 127.7, 127.6, 94.0 (d, *J*=184.1 Hz), 77.4, 75.4 (d, *J*=17.1 Hz), 73.4, 72.4, 71.0,

52.8 (d, J=21.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −179.1 (ddd, J=32.1, 22.0, 10.4 Hz, 1F); IR (KBr) ν_{max} 3440, 3030, 2863, 1496, 1454, 1209, 1072 cm^{-1}; MS (ESI) m/z 360 $(M+NH_4)^+$; HRMS calcd for $C_{21}H_{23}FO_3Na$: 365.1529; found: 365.1523.

*4.2.7. (1S,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl methyl carbonate(**14**).* To a stirred solution of **12** (62 mg, 0.183 mmol) and pyridine (59 μL, 0.732 mmol) in CH_2Cl_2 (2 mL) was added methyl chloroformate (57 μL, 0.732 mmol) dropwise at 0 °C. The reaction mixture was then stirred at 0 °C for 60 min. The solvent was removed in vacuo, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate=8:1) on silica gel to give carbonate **14** (68 mg, 93% yield) as a clear oil: $[\alpha]_{D^{25}}$ −20.5° (*c* 1.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.23 (m, 10H), 6.02 (d, J=6.3 Hz, 1H), 5.79 (d, J=6.3 Hz, 1H), 5.66 (d, J=20.7 Hz, 1H), 5.03 (dt, J=51.6, 3.6 Hz, 1H), 4.75–4.54 (m, 4H), 3.79 (s, 3H), 3.67–3.62 (m, 3H), 3.1 (d, J=25.2 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.2, 138.1, 138.0, 135.2, 135.2, 128.5, 128.4127.9, 127.7, 127.7, 99.1 (d, J=185.8 Hz), 86.5 (d, J=29.5 Hz), 77.7, 73.5, 72.6, 70.8, 55.0, 52.5 (d, J=22.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −186.4 (ddd, J=45.7, 25.7, 21.2 Hz, 1F); IR (KBr) ν_{max} 3064, 3030, 2955, 2863, 1752, 1442, 1269, 697 cm^{-1}; MS(ESI) m/z 418 $(M+NH_4)^+$; HRMS calcd for $C_{23}H_{25}FO_5Na$: 423.1584; found: 423.1578.

*4.2.8. (1R,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl methyl carbonate(**15**).* Using the same conditions as described for compound **14**, compound **15** (115 mg, 96%) was prepared as a clear oil from compound **13** (103 mg, 0.30 mmol): $[\alpha]_{D^{25}}$ −48.6° (*c* 1.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 10H), 6.08 (s, 1H), 5.87 (s, 1H), 5.02 (d, J=53.1 Hz, 1H), 4.76–4.53 (m, 4H), 3.79 (s,3H), 3.78 (m, 1H), 3.63 (d, J=3.3 Hz, 2H), 3.27 (d, J=20.7 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.3, 138.0, 137.9, 135.8, 135.7, 128.2, 128.0, 127.9, 127.8, 127.7, 91.6 (d, J=194.0 Hz), 79.0 (d, J=14.9 Hz), 73.5, 72.5, 71.0, 54.9, 52.4 (d, J=21.2 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −199.6 (ddd, J=26.5, 21.1, 5.4 Hz, 1F); IR (KBr) ν_{max} 3063, 3031, 2955, 2863, 1746, 1441, 1262, 696 cm^{-1}; MS (ESI) m/z 418 $(M+NH_4)^+$; HRMS calcd for $C_{23}H_{25}FO_5Na$: 423.1584; found: 423.1578.

*4.2.9. 9-((1R,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl)-6-chloro-9H-purine(**16**).* To a mixture of compound **12** (69 mg, 0.204 mmol), 6-chloropurine (64 mg, 0.416 mmol), and PPh_3 (142 mg, 0.541 mmol) in dry THF (2 mL) was added DEAD (95 mg, 0.546 mmol) slowly at 0 °C. Then the reaction mixture was warmed to room temperature and stirred overnight. The solvent was removed in vacuo, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate=3:1) on silica gel to give compound **16** as a pale yellow oil (47 mg, 48% yield): $[\alpha]_{D^{25}}$−42.4° (*c* 0.90, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.05 (d, J=2.4 Hz, 1H), 7.40–7.31 (m, 10H), 6.22 (d, J=5.7 Hz, 1H), 6.02 (d, J=17.7 Hz), 5.95 (d, J=5.7 Hz, 1H), 5.07 (dd, J=52.8, 5.4 Hz, 1H), 4.78–4.54 (m, 4H), 3.91 (dd, J=9.6, 4.5 Hz, 1H), 3.69–3.58 (m, 2H), 3.40 (d, J=27.3 Hz, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 152.1, 151.9, 150.9, 144.9, 137.7, 137.6, 135.2, 131.5, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 93.3 (d, J=190.5 Hz), 73.7, 72.4, 70.2, 60.8 (d, J=16.9 Hz), 54.6 (d, J=21.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −188.3 (ddd, J=44.0, 25.4, 18.0 Hz, 1F); IR (KBr) ν_{max} 3064, 2864, 1776, 1699, 1591, 1561, 1402, 1336, 1200, 1102 cm^{-1}; MS (ESI) m/z 479$(M+H)^+$, 501$(M+Na)^+$; HRMS calcd for $C_{26}H_{25}N_4O_2FCl$: 479.1650; found: 479.1645.

*4.2.10. 9-((1S,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl)-6-chloro-9H-purine(**17**).* Using the same conditions as described for compound **16**, compound **17** (66 mg, 55%) was prepared as a pale yellow oil from compound **13** (86 mg, 0.25 mmol): $[\alpha]_{D^{25}}$ −18.0°(*c* 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.05 (s, 1H), 7.39–7.00 (m, 10H), 6.27 (d, J=4.8 Hz, 1H), 5.86 (d, J=6.0 Hz, 1H), 5.66 (d, J=22.2 Hz, 1H), 4.93 (d, J=51.9 Hz, 1H), 4.61–4.40 (m, 4H), 3.82–3.34 (m, 2H), 3.29 (d, J=30.0 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 152.1, 151.3 (d, J=44.3 Hz), 143.9, 137.6, 137.1, 136.7, 128.5, 128.3, 128.2, 127.9, 126.1, 100.5 (d, J=190.0 Hz), 73.6, 72.3, 70.1, 65.7 (d, J=31.9 Hz), 54.4 (d, J=23.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −176.6 (ddd, J=50.5, 27.4, 22.6 Hz, 1F); IR (KBr) ν_{max} 2921, 2855, 1748, 1733, 1590, 1561, 1336, 1196, 1122, 1095 cm^{-1}; MS (ESI) m/z 479 $(M+H)^+$, 501 $(M+Na)^+$; HRMS calcd for $C_{26}H_{24}N_4O_2FClNa$: 501.1470; found: 501.1464.

*4.2.11. 9-((1R,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl)-9H-purin-6-amine(**18**).* Compound **16** (50 mg, 0.105 mmol) was dissolved in NH_3/MeOH (2 mL) in a sealed tube and heated at 80 °C for 12 h. The solvent was then removed in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH=20:1) on silica gel to give compound **18** as a white solid (41 mg, 86% yield): mp 193 °C; $[\alpha]_{D^{25}}$ −25.49° (*c* 1.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.74 (s, 1H), 7.39–7.35 (m, 10H), 6.19 (d, J=5.1 Hz, 1H), 5.97–5.92 (m, 2H), 5.78 (s, 2H), 5.07 (dd, J=54.0, 5.7 Hz, 1H), 4.76–4.52 (m, 4H), 3.85(dd, J=10.2, 5.1 Hz, 1H), 3.67–3.59 (m, 2H), 3.36 (d, J=24.0 Hz); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 152.1151.9, 150.9, 144.9, 137.7, 137.6, 135.2, 131.5, 128.7, 128.6, 128.3, 128.2, 128.0, 127.8, 93.3 (d, J=190.5 Hz), 73.7, 72.4, 70.2, 60.8 (d, J=16.9 Hz), 54.6 (d, J=21.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −188.3 (ddd, J=44.0, 25.4, 18.0 Hz, 1F); IR (KBr) ν_{max} 3311, 2922, 2851, 1647, 1597, 1473, 1096, 698 cm^{-1}; MS (ESI) m/z 479 $(M+H)^+$, 501 $(M+Na)^+$; HRMS calcd for $C_{26}H_{27}N_5O_2F$: 460.2143; found: 460.2133.

*4.2.12. 9-((1S,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl)-9H-purin-6-amine(**19**).* Using the same conditions as described for compound **18**, compound **19** (58 mg, 80%) was prepared as a white solid from compound **17** (72 mg, 0.15 mmol): mp 201 °C; $[\alpha]_{D^{25}}$ −13.2°(*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.74 (s, 1H), 7.40–7.07 (m, 10H), 6.31 (s, 2H), 6.22 (d, J=5.7 Hz, 1H), 5.84 (d, J=5.1 Hz, 1H), 5.74 (d, J=23.1 Hz, 1H), 4.98 (d, J=51.6 Hz, 1H), 4.67–4.44 (m, 4H), 3.80–3.77 (m, 1H), 3.68 (s, 2H), 3.27 (d, J=27.0 Hz, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 155.6, 152.9, 149.8, 138.9, 137.7, 137.3, 135.5, 128.4, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 126.8, 119.6, 100.8 (d, J=86.7 Hz), 73.5, 72.2, 70.3, 65.0 (d, J=30.7 Hz), 54.1 (d, J=23.2 Hz), 29.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −177.8 (ddd, J=50.5, 27.1, 22.0 Hz, 1F); IR (KBr) ν_{max} 3311, 3171, 2922, 2851, 1647, 1597, 1473, 1328, 1096, 698 cm^{-1}; MS (ESI) m/z 460 $(M+H)^+$, 482 $(M+Na)^+$; HRMS calcd for $C_{26}H_{27}N_5O_2F$: 460.2149; found: 460.2143.

*4.2.13. (S)-1-((1S,4R,5S)-4-(6-Amino-9H-purin-9-yl)-5-fluorocyclopent-2-enyl)ethane-1,2-diol(**20**).* To a solution of compound **18** (34 mg, 0.074 mmol) in anhydrous CH_2Cl_2 (3 mL) was added BCl_3 (1 M in CH_2Cl_2, 0.75 mL, 0.75 mmol) at −30 °C. After the reaction mixture was stirred for 2 h, the mixture was quenched with MeOH (2 mL), and the solvent was removed in vacuo. The residue was purified by silica gel column (CH_2Cl_2/MeOH=12:1) to give compound **20** as a foam (19 mg, 90% yield): $[\alpha]_{D^{25}}$ −101.2°(*c* 0.36, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.45 (s, 1H), 8.25 (s, 1H), 6.37 (d, J=4.5 Hz, 1H), 6.11(d, J=6.0 Hz, 1H), 5.99 (d, J=16.8 Hz, 1H), 5.36 (dd, J=53.1, 4.2 Hz, 1H), 3.96 (dd, J=10.5, 5.1 Hz, 1H), 3.61 (d, J=5.7 Hz, 2H), 3.35 (d, J=11.7 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 156.6, 151.7, 147.6, 142.4, 141.9, 133.9, 125.7, 116.9, 91.9 (d, J=194.3 Hz), 70.0 (d, J=6.3 Hz), 62.4, 59.6, 53.0 (d, J=21.2 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −191.6 (ddd, J=40.6, 25.9, 14.7 Hz, 1F); IR (KBr) ν_{max} 3422, 1686, 1497, 1416, 1228, 1095 cm^{-1}; MS (ESI) m/z 280 $(M+H)^+$; HRMS calcd for $C_{12}H_{15}FN_5O_2$: 280.1210; found: 280.1204.

*4.2.14. (S)-1-((1S,4S,5S)-4-(6-Amino-9H-purin-9-yl)-5-fluorocyclopent-2-enyl)ethane-1,2-diol(**21**).* Using the same conditions as described for compound **20**, compound **21** (31 mg, 94%) was prepared as a foam from compound **19** (57 mg, 0.12 mmol): $[\alpha]_{D^{25}}$ 4.5° (*c* 1.50, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.77 (s, 1H), 8.68

(s, 1H), 6.65 (d, *J*=5.1 Hz, 1H), 6.30 (d, *J*=5.7 Hz, 1H), 6.16 (d, *J*=22.5 Hz, 1H), 5.58 (d, *J*=51.9 Hz, 1H), 4.16 (dd, *J*=10.5, 5.7 Hz, 1H), 3.95 (d, *J*=6.0 Hz, 2H), 3.52 (d, *J*=27.9 Hz, 1H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 150.3, 148.8, 143.7, 142.8, 135.7, 126.5, 118.6, 100.8 (d, *J*=186.9 Hz), 71.5, 66.0 (d, *J*=31.7 Hz), 63.9, 54.3 (d, *J*=22.4 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −178.8 (m, 1F); IR (KBr) ν_{max} 3415, 1712, 1608, 1557, 1379, 1143, 1095, 600 cm^{-1}; MS(ESI) *m*/*z* 280 $(M+H)^+$; HRMS calcd for $C_{12}H_{15}FN_5O_2$: 280.1210; found: 280.1204.

*4.2.15. ((1S,4R,5S)-4-(6-Amino-9H-purin-9-yl)-5-fluorocyclopent-2-enyl)methanol(**22**).* Compound **20** was dissolved in methanol (1 mL), followed by treatment with a solution of saturated $NaIO_4$ (0.2 mL) at room temperature with stirring. After the reaction mixture was stirred for 15 min, $NaBH_4$ (22 mg, 0.585 mmol) was added in portions at 0 °C, and the mixture was stirred at 0 °C for 1 h. Then the reaction was quenched by aqueous NH_4Cl, extracted with EtOAc, dried by Na_2SO_4. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH=15:1) on silica gel to give **22** as a white solid (11 mg, 75% yield): mp 190 °C; $[\alpha]_{D^{25}}$ −28.9°(*c* 0.85, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.24 (s,1H), 8.02 (s, 1H), 6.24 (s, 1H), 6.06 (d, *J*=3.9 Hz, 1H), 5.87 (d, *J*=15.3 Hz, 1H), 5.26 (dd, *J*=53.1, 4.2 Hz, 1H), 3.82–3.62 (m, 2H), 3.22 (d, *J*=24.6 Hz, 1H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 155.8, 152.2, 149.5, 140.5, 136.1, 127.4, 118.4, 92.6 (d, *J*=189.6 Hz), 60.6 (d, *J*=36.8 Hz), 54.5 (d, *J*=20.6 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −193.0 (ddd, *J*=39.8, 25.1, 15.8 Hz, 1F); IR (KBr) ν_{max} 3410, 3185, 2925, 1648, 1602, 1477, 1068 cm^{-1}; MS (ESI) *m*/*z* 250 $(M+H)^+$; HRMS calcd for $C_{11}H_{13}FN_5O$: 250.1104; found: 250.1099.

*4.2.16. ((1S,4S,5S)-4-(6-Amino-9H-purin-9-yl)-5-fluorocyclopent-2-enyl)methanol(**23**).* Using the same conditions as described for compound **22**, compound **23** (17 mg, 79%) was prepared as a white solid from compound **21** (25 mg, 0.09 mmol): mp 188 °C; $[\alpha]_{D^{25}}$ 32.6°(*c* 0.80, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 8.63 (s, 1H), 8.52 (s, 1H), 6.59 (d, *J*=5.4 Hz, 1H), 6.35 (d, *J*=5.4 Hz, 1H), 5.60 (d, *J*=52.2 Hz, 1H), 4.22–4.11 (m,2H), 3.52 (d, *J*=27.3 Hz, 1H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 157.7, 154.1, 150.9, 141.3, 138.2, 128.6, 120.6, 101.9 (d, *J*=186.1 Hz), 67.5 (d, *J*=30.7 Hz), 62.9 (d, *J*=4.7 Hz), 56.0 (d, *J*=22.3 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −179.1 (m, 1F); IR (KBr) ν_{max} 3436, 1679, 1606, 1470, 1414, 1296, 1094 cm^{-1}; MS(ESI) *m*/*z* 250 $(M+H)^+$; HRMS calcd for $C_{11}H_{13}FN_5O$: 250.1104; found: 250.1099.

*4.2.17. 1-((1R,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl)pyrimidine-2,4(1H,3H)-dione (**24**).* To a mixture of compound **13** (69 mg, 0.204 mmol), 3-benzoyl uracil (64 mg, 0.416 mmol), and PPh_3 (142 mg, 0.541 mmol) in dry THF (2 mL) was added DEAD (95 mg, 0.546 mmol) slowly at 0 °C. Then the reaction mixture was warmed to room temperature and stirred overnight. The solvent was then removed in vacuo, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate=3:1) on silica gel to give the crude product. To a solution of the crude product in MeOH (3 mL) was added NH_3/MeOH (3 mL) and the reaction mixture was stirred at room temperature for 2 h. Then The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (CH_2Cl_2/MeOH=20:1) on silica gel to give **24** as a yellow oil (36 mg, 40% yield for two steps): $[\alpha]_{D^{25}}$−36.4° (*c* 1.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (s, 1H), 7.84 (d, *J*=7.5 Hz, 1H), 7.82–7.26 (m, 10H), 7.10 (d, *J*=7.5 Hz, 1H), 6.28 (s, 1H), 6.11 (s, 1H), 5.74–5.65 (m, 2H), 5.02 (dd, *J*=52.8, 5.1 Hz, 1H), 4.71–4.49 (m, 1H), 4.21 (dd, *J*=8.4, 3.6 Hz), 3.96 (ddd, *J*=14.7, 10.2, 4.8 Hz, 2H), 3.26 (d, *J*=28.2 Hz, 1H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 169.8, 163.9, 151.2, 142.6, 137.7, 137.5, 135.0, 133.4, 132.0, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.4, 101.2, 93.6 (d, *J*=188.6 Hz), 73.6, 72.4, 70.2, 62.3 (d, *J*=16.2 Hz), 54.7 (d, *J*=22.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −188.2 (ddd, *J*=45.4, 25.9, 18.3 Hz, 1F); IR (KBr) ν_{max} 3381, 3185, 1645, 1576, 1385, 1107, 698 cm^{-1}; MS (ESI) *m*/*z* 437 $(M+H)^+$; HRMS calcd for $C_{25}H_{25}FN_2O_4Na$: 459.1696; found: 459.1691.

*4.2.18. 1-((1R,4S,5S)-4-((S)-1,2-Bis(benzyloxy)ethyl)-5-fluorocyclopent-2-enyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**25**).* Using the same conditions as described for compound **24**, compound **25** (33 mg, 37%) was prepared as a yellow oil from compound **12** (68 mg, 0.2 mmol): $[\alpha]_{D^{25}}$ 18.5°(*c* 0.35,$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.37–7.31 (m, 10H), 6.93 (s, 1H), 6.12 (d, *J*=5.4 Hz, 1H), 5.77 (d, *J*=20.7 Hz, 1H), 5.75 (d, *J*=5.4 Hz, 1H), 5.02 (dd, *J*=53.1, 5.4 Hz, 1H), 4.71–4.49 (m, 4H), 3.83 (dd, *J*=10.2, 5.4 Hz), 3.59 (ddd, *J*=15.0, 10.2, 4.8 Hz, 1H), 3.27 (d, *J*=27.6 Hz, 1H), 1.89(s, 3H); ^{13}C NMR (100.7 MHz, $CDCl_3$) δ 164.2, 151.3, 138.4, 138.4, 137.7, 137.5, 134.7, 128.7, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 109.6, 93.7 (d, *J*=188.2 Hz), 73.6, 72.5, 70.3, 62.0 (d, *J*=16.2 Hz), 54.7 (*J*=22.1 Hz), 12.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ −189.7 (ddd, *J*=45.7, 27.1, 18.0 Hz, 1F); IR (KBr) ν_{max} 3186, 3032, 2925, 2863, 1689, 1454, 1261, 1101, 746, 699 cm^{-1}; MS (ESI) *m*/*z* 451 $(M+H)^+$; HRMS calcd for $C_{26}H_{27}FN_2O_4Na$: 473.1853; found: 473.1847.

*4.2.19. 1-((1R,4S,5S)-4-((S)-1,2-Dihydroxyethyl)-5-fluorocyclopent-2-enyl)pyrimidine-2,4(1H,3H)-dione (**26**).* Using the same conditions as described for compound **20**, compound **26** (27 mg, 95%) was prepared as a yellow oil from compound **24** (48 mg, 0.11 mmol): $[\alpha]_{D^{25}}$ −21.0° (*c* 0.65, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.29 (d, *J*=6.9 Hz, 1H), 6.14 (d, *J*=3.3 Hz, 1H), 5.78 (d, *J*=6.3 Hz, 1H), 5.71 (d, *J*=17.1 Hz, 1H), 5.65 (d, *J*=7.5 Hz, 1H), 5.40 (s, 1H), 5.11 (dd, *J*=53.1, 5.4 Hz, 1H), 3.78 (dd, *J*=10.5, 4.5 Hz, 1H), 3.45 (d, *J*=5.7 Hz, 1H), 3.20 (d, *J*=28.2 Hz, 1H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 165.3, 151.8, 143.6, 134.8, 128.2, 100.3, 93.9 (d, *J*=187.4 Hz), 71.9 (d, *J*=8.3 Hz), 64.2, 62.6 (d, *J*=16.2 Hz), 55.1 (d, *J*=21.2 Hz), 53.6; ^{19}F NMR (282 MHz, CD_3OD) δ −190.9 (ddd, *J*=44.0, 27.9, 16.4 Hz, 1F); IR (KBr) ν_{max} 3428, 2995, 1688, 1664, 1466, 1412, 1260, 1047 cm^{-1}; MS (ESI) *m*/*z* 257 $(M+H)^+$; HRMS calcd for $C_{11}H_{13}FN_2O_4Na$: 279.0757; found: 279.0752.

*4.2.20. 1-((1R,4S,5S)-4-((S)-1,2-Dihydroxyethyl)-5-fluorocyclopent-2-enyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**27**).* Using the same conditions as described for compound **20**, compound **27** (23 mg, 92%) was prepared as a foam from compound **25** (48 mg, 0.11 mmol): $[\alpha]_{D^{25}}$ −43.0°(*c* 0.90, CH_3OH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.08 (s, 1H), 6.12 (d, *J*=5.4 Hz, 1H), 5.78 (d, *J*=6.0 Hz, 1H), 5.57 (d, *J*=13.8 Hz, 1H), 5.09 (dd, *J*=53.4, 5.4 Hz, 1H), 3.79 (dd, *J*=10.5, 6.0 Hz), 3.45–3.21 (m, 4H), 3.13 (s, 1H), 3.04 (s, 1H), 1.75 (s, 3H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 165.2, 151.7, 139.1, 134.4, 128.2, 108.8, 93.7 (d, *J*=187.4 Hz), 71.7 (d, *J*=8.0 Hz), 64.0, 62.2 (d, *J*=15.4 Hz), 54.9 (d, *J*=21.0 Hz), 10.9; ^{19}F NMR (282 MHz, CD_3OD) δ −191.0 (ddd, *J*=44.0, 27.9, 16.6 Hz, 1F); IR (KBr) ν_{max} 3413, 1686, 1655, 1461, 1383, 1257, 999 cm^{-1}; MS (ESI) *m*/*z* 271 $(M+H)^+$; HRMS calcd for $C_{12}H_{15}FN_2O_4Na$: 293.0932; found: 293.0908.

*4.2.21. 1-((1R,4S,5S)-5-Fluoro-4-(hydroxymethyl)cyclopent-2-enyl) pyrimidine-2,4(1H,3H)-dione (**28**).* Using the same conditions as described for compound **22**, compound **28** (16 mg, 80%) was prepared as a sticky oil from compound **26**(23 mg, 0.09 mmol): $[\alpha]_{D^{25}}$ 0.9° (*c* 0.65, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.28 (d, *J*=6.3 Hz, 1H), 6.06 (t, *J*=3.0 Hz, 1H), 5.75 (d, *J*=6.0 Hz, 1H), 5.58 (d, *J*=18.0 Hz, 1H), 5.54 (d, *J*=8.1 Hz, 1H), 5.05 (dd, *J*=52.8, 5.1 Hz, 1H), 3.63 (dd, *J*=11.1, 4.8 Hz, 1H), 3.45 (dd, *J*=11.1, 6.0 Hz, 1H), 3.00 (d, *J*=26.4 Hz, 1H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 170.6, 159.7 (dd, *J*=63.4, 31.5 Hz), 132.7, 131.8, 129.6, 128.5, 128.3, 127.9, 127.7, 126.5, 126.2, 126.2, 125.6, 125.1, 124.7, 123.7, 118.5 (d, *J*=299.8 Hz),35.3 (d, *J*=224.9 Hz); ^{19}F NMR (282 MHz, CD_3OD) δ −192.2 (ddd, *J*=43.4, 25.9, 17.5 Hz, 1F); IR (KBr) ν_{max} 3428, 1713, 1665, 1284, 1221, 1070,

958 cm^{-1}; MS (ESI) *m*/*z* 227 $(M+H)^+$; HRMS calcd for $C_{10}H_{12}FN_2O_3$: 227.0832; found: 227.0827.

*4.2.22. 1-((1R,4S,5S)-5-Fluoro-4-(hydroxymethyl)cyclopent-2-enyl)-5-methylpyrimidine-2,4(1H,3H)-dione (**29**).* Using the same conditions as described for compound **22**, compound **29** (16 mg, 82%) was prepared a sticky oil from compound **27** (22 mg, 0.08 mmol): $[\alpha]_{D^{25}}$ −12.9°(*c* 0.65, CH_3OH); ^1H NMR (300 MHz, CD_3OD) δ 7.13 (s, 1H), 6.12 (d, *J*=6.3 Hz, 1H), 5.81 (d, *J*=5.7 Hz, 1H), 5.61 (d, *J*=18.6 Hz, 1H), 5.09 (dd, *J*=52.5, 4.8 Hz, 1H), 3.68 (dd, *J*=11.1, 4.5 Hz, 1H), 3.50 (dd, *J*=11.1, 6.3 Hz, 1H), 3.06 (d, *J*=26.7 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (100.7 MHz, CD_3OD) δ 165.2, 151.7, 139.1, 135.8, 127.6, 108.8, 92.8 (d, *J*=187.9 Hz), 62.3 (d, *J*=16.3 Hz), 60.8 (d, *J*=9.3 Hz), 54.8 (d, *J*=21.0 Hz), 10.8; ^{19}F NMR (282 MHz, CD_3OD) δ −192.1 (ddd, *J*=44.3, 26.5, 18.0 Hz, 1F); IR (KBr) ν_{max} 3448, 2926, 1691, 1469, 1388, 1258 cm^{-1}; MS (ESI) *m*/*z* 241 $(M+H)^+$; HRMS calcd for $C_{11}H_{13}FN_2O_3Na$: 263.0808; found: 263.0802.

Acknowledgements

We thank National Natural Science Foundation of China (21072028, 20832008) for funding this work.

References and notes

1. For review, see: (a) Casu, F.; Chiacchio, M. A.; Romeo, R.; Gumina, G. *Curr. Org. Chem.* **2007**, *11*, 999; (b) Jeong, L.; Lee, J. *Antiviral Chem. Chemother.* **2004**, *15*, 235; (c) Zhu, X. F. *Nucleosides, Nucleotides Nucleic Acids* **2000**, *19*, 651; (d) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319; (e) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229; (f) Marquez, V. E. *Adv. Antiviral Drug Des.* **1996**, *2*, 89.
2. Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17.
3. (a) Weller, S.; Radomski, K. M.; Lou, Y.; Stein, D. S. *Antimicrob. Agents Chemother.* **2000**, *44*, 2052; (b) Daluge, S.; Good, S.; Faletto, M.; Miller, W.; St. Clair, M.; Boone, L.; Tisdale, M.; Parry, N.; Reardon, J.; Dornsife, R.; Averett, D.; Krenitsky, T. *Antimicrob. Agents Chemother.* **1997**, *41*, 1082.
4. (a) Yin, X.-Q.; Schneller, S. W. *Tetrahedron Lett.* **2005**, *46*, 7535; (b) Moon, H. R.; Lee, H. J.; Kim, K. R.; Lee, K. M.; Lee, S. K.; Kim, H. O.; Chun, M. W.; Jeong, L. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5641; (c) Kim, H. O.; Yoo, S. J.; Ahn, H. S.; Choi, W. J.; Moon, H. R.; Lee, K. M.; Chun, M. W.; Jeong, L. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2091; (d) Jeong, L. S.; Yoo, S. J.; Lee, K. M.; Koo, M. J.; Choi, W. J.; Kim, H. O.; Moon, H. R.; Lee, M. Y.; Park, J. G.; Lee, S. K.; Chun, M. W. *J. Med. Chem.* **2003**, *46*, 201; (e) Wachtmeister, J.; Classon, B.; Samuelsson, B. *Tetrahedron* **1997**, *53*, 1861; (f) Payne, A. N.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2633; (g) Highcock, R. M.; Hilpert, H.; Myers, P. L.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1127; (h) Coe, D. M.; Parry, D. M.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2373; (i) Coe, D. M.; Myers, P. L.; Parry, D. M.; Roberts, S. M.; Storerb, R. *J. Chem. Soc., Chem. Commun.* **1990**, 151; (j) Borthwick, A. D.; Evans, D. N.; Kirk, B. E.; Biggadike, K.; Exall, A. M.; Youds, P.; Roberts, S. M.; Knight, D. J.; Coates, J. A. V. *J. Med. Chem.* **1990**, *33*, 179; (k) Fletcher, C. A.; Hilpert, H.; Myers, P. L.; Roberts, S. M.; Storer, R. *J. Chem. Soc., Chem. Commun.* **1989**, 1707; (l) Madhavan, G. V. B.; McGee, D. P. C.; Rydzewski, R. M.; Boehme, R.; Martin, J. C.; Prisbe, E. J. *J. Med. Chem.* **1988**, *31*, 1798; (m) Biggadike, K.; Borthwick, A. D.; Exall, A. M.; Kirk, B. E. K.; Roberts, S. M.; Youds, P.; Slawin, A. M. Z.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1987**, 255.
5. Hamamoto, Y.; Nakashima, H.; Matsui, T.; Matsuda, A.; Ueda, T.; Yamamoto, N. *Antimicrob. Agents Chemother.* **1987**, *31*, 907.
6. (a) Trost, B. M.; Madsen, R.; Guile, S. D. *Tetrahedron Lett.* **1997**, *38*, 1707; (b) Trost, B. M.; Madsen, R.; Guile, S. G.; Elia, A. E. H. *Angew. Chem., Int. Ed.* **1996**, *35*, 1569.
7. For review, see: Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551.
8. For review about metathesis in nucleoside chemistry, see: Amblard, F.; Nolan, S. P.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 7067.
9. (a) Araki, K.; Welch, J. T. *Tetrahedron Lett.* **1993**, *34*, 2251; (b) Welch, J. T.; Plummer, J. S.; Chou, T. S. *J. Org. Chem.* **1991**, *56*, 353; (c) Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663.
10. (a) Marais, J. S. C. *Onderstepoort J. Vet. Sci. Anim. Ind.* **1944**, *20*, 67; (b) Marais, J. S. C. *Onderstepoort J. Vet. Sci. Anim. Ind.* **1943**, *18*, 203; (c) Anderson, W. B.; Board, P. G.; Gargano, B.; Anders, M. W. *Chem. Res. Toxicol.* **1999**, *12*, 1144; (d) Tong, Z.; Board, P. G.; Anders, M. W. *Chem. Res. Toxicol.* **1998**, *11*, 1332.
11. (a) Zheng, F.; Zhang, X.; Qing, F.-L. *Chem. Commun.* **2009**, 1505; (b) Yang, Y.-Y.; Xu, J.; You, Z.-W.; Xu, X.-H.; Qiu, X.-L.; Qing, F.-L. *Org. Lett.* **2007**, *9*, 5437; (c) Yang, Y.-Y.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 4257.
12. Crystal data have been deposited at the Cambridge Crystallographic Data Center with reference number: CCDC 805686.