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Stereoselective synthesis and anti-HCV activity of conformationally restricted 2′-*C*-substituted carbanucleosides

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ABSTRACT

Conformationally restricted 2′-*C*-azido-, hydroxy- and fluoromethyl-carbanucleosides **4b**–**f** were efficiently synthesized via the stereoselective conversion of ketone **7** to epoxide **14**, followed by the stereoselective opening of the epoxide with nucleophiles (OAc, N_3, and F), while the corresponding 2′-*C*-methyl-carbanucleoside **4a** was synthesized via the stereoselective Grignard reaction of ketone **7** with methylmagnesium iodide as a key step. All the final nucleosides **4a**–**f** were assayed for anti-HCV activity, but showed neither significant anti-HCV activity nor cytotoxicity in a cell-based replicon assay.

1. Introduction

Hepatitis C is a lethal viral disease caused by the hepatitis C virus (HCV), and 3% of the world's population is infected with this virus.[1–3] Chronic infection with HCV causes the gradual development of liver cirrhosis and can lead to hepatocellular carcinoma (HCC),[1–3] making an effective cure for this disease highly desirable. Interferon-α or pegylated-interferon-α in combination with ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide) has been the only approved therapy[4,5] for the treatment of HCV-infected individuals, but boceprevir[6] and telaprevir[7] were recently approved by the FDA as new HCV protease inhibitors.

HCV has a positive-sense single-stranded RNA genome that is replicated by the RNA-dependent RNA polymerase of NS5B to produce a negative-sense strand RNA.[8] Because the inhibition of the RNA-dependent RNA polymerase prevents the replication of HCV, this enzyme serves as an attractive target for the development of new anti-HCV agents.

Many classes of nucleoside and non-nucleoside derivatives have been synthesized as anti-RNA-dependent RNA polymerase inhibitors.[9,10] Non-nucleoside derivatives inhibit the replication of HCV by noncompetitively binding to the allosteric site of the enzyme,[11] while nucleoside derivatives bind to the catalytic site, leading to reversible competitive inhibition and/or RNA chain termination.[12] In particular, nucleoside derivatives, such as 2′-*C*-methyladenosine (**1**) and 2′-*C*-methylguanosine (**2**) exhibited highly potent anti-HCV activities (EC_{50}=0.26 μM and 3.5 μM, respectively) in a cell-based replicon assay (Fig. 1).[13] These nucleosides are converted into the corresponding triphosphates, which compete with natural nucleoside triphosphates (NTPs).[12] It has been reported that the 2′-methyl group plays a crucial role in causing RNA chain termination by hindering the incorporation of the incoming natural NTP substrate.[14]

Based on the potent anti-HCV activity of 2′-*C*-methylribofuranosyl nucleosides **1** and **2**, the corresponding 2′-*C*-hydroxymethylribofuranosyl nucleosides were designed and synthesized, and among these derivatives the adenine derivative **3** showed potent anti-HCV activity in a cell-based replicon assay.[15] These results indicate that the hydroxyl of the 2′-*C*-hydroxymethyl group induced favourable interactions with the HCV RNA polymerase. These interactions could be the results of compound **3** adopting the same Northern C3′-*endo* conformation as compounds **1** and **2**.[13] It is well known that bicyclo[3.1.0]hexane nucleosides lock in extreme North and South conformations, contrary to the normal ribose ring of

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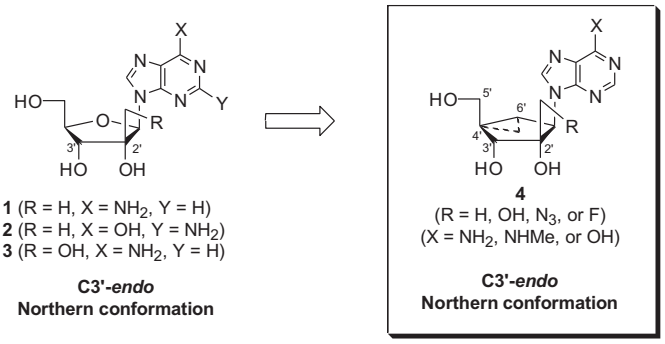


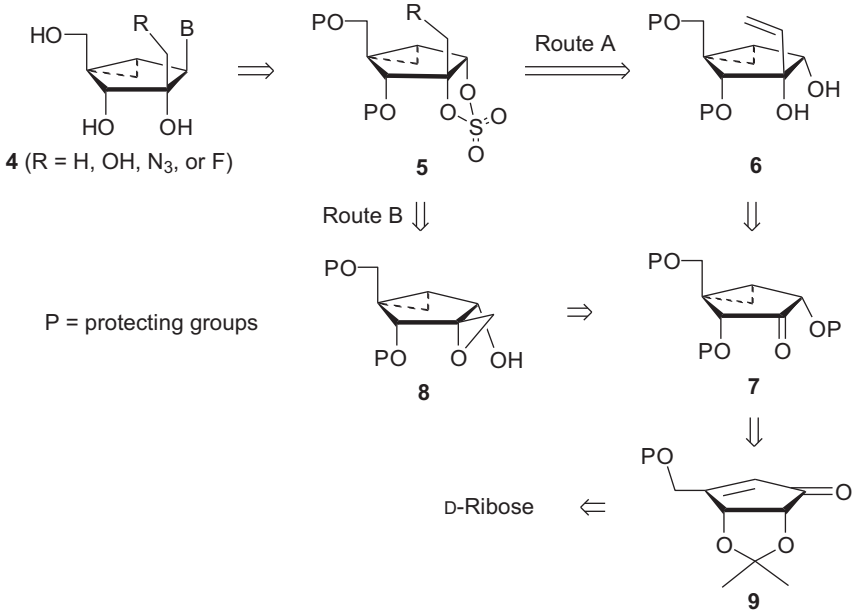
Fig. 1. The rationale for the design of the target nucleosides.

nucleosides, which are in a dynamic N/S equilibrium.[16] In bicyclo [3.1.0]hexane nucleosides **4**, the cyclopropane ring is fused between C4′ and C6′, which is presumed to cause the same Northern C3′-*endo* conformation as anti-HCV compound **3**.[17] Because of this similarity, we designed and synthesized conformationally locked nucleosides **4** (Fig. 1). The key step for the synthesis of the target nucleosides was to introduce a 2′-*C*-hydroxymethyl group, which was achieved by the stereoselective conversion of the ketone to the epoxide, not by the vinyl Grignard reaction to the ketone used in the introduction of a 2′-*C*-methyl moiety.[18] Herein, we report full accounts of the stereoselective synthesis of conformationally locked 2′-*C*-substituted carbanucleosides **4** and their anti-HCV activity.

2. Results and discussion

2.1. Chemistry

Scheme 1 illustrates the synthetic strategy used to obtain target nucleosides **4**. The desired nucleosides **4** could be synthesized using the cyclic sulfate **5** as the glycosyl donor surrogate.

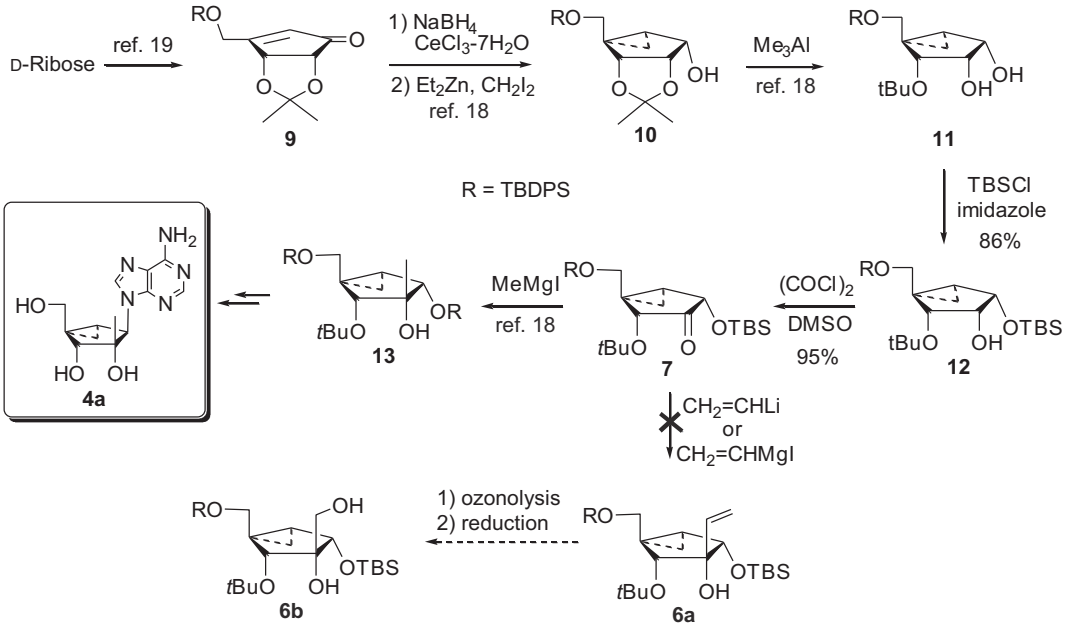


Scheme 1. Retrosynthesis of the final nucleosides **4**.

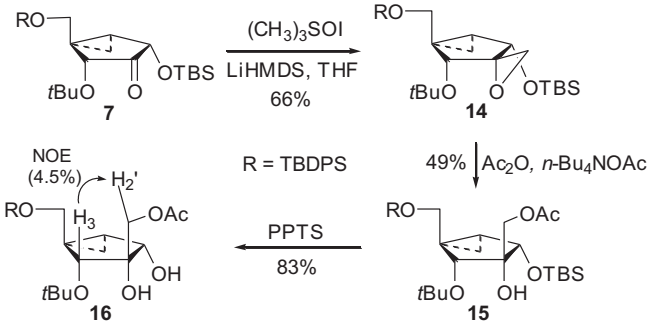
The 2′-*C*-substituted-methyl moiety (R=OH, N_3, or F) can be derived by the manipulation of the vinyl derivative **6**, which could be obtained from stereoselective vinyl addition to the ketone **7** (route A), as used in the preparation of 2′-*C*-methyl carbocyclic nucleoside (R=H).[18] Additionally, the 2′-*C*-substituted-methyl moiety can be efficiently introduced from the opening of the epoxide **8** with nucleophiles, such as OAc, N_3, and F ions (route B). Epoxide **8** could in turn be derived from the ketone **7** using the sulfur ylide. Ketone **7** could be synthesized from D-ribose via the cyclopentenone derivative **9**,[19]according to our previously published procedure.[18]

Our synthesis started with known cyclopentenone **9**,[19] which was efficiently synthesized from D-ribose (Scheme 2). The cyclopentenone **9** was converted to known *tert*-butyl diol **11**.[18] Luche[20] reduction of cyclopentenone **9** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ gave α-allylic alcohol as a single diastereomer, in which the delivery of the hydride occurred from the less hindered convex face of the ketone.[18,21] The Simmons–Smith cyclopropanation of α-allylic alcohol with diethyl zinc and methylene iodide produced known cyclopropyl-fused alcohol**10**[18] as a single diastereomer, due to the directing effect of the allylic hydroxyl group.[22] Regioselective cleavage of **10** with trimethylaluminum[23] produced known diol **11**.[18] Selective protection of 1-hydroxyl group in **11** with TBS group followed by Swern oxidation afforded the key intermediate **7**.[18] As mentioned in Scheme 1, the first trial (route A) to introduce the 2-*C*-hydroxymethyl group included stereoselective vinylation followed by ozonolysis and reduction, but this route failed to give the desired product **6b**. Treatment of ketone **7** with vinylmagnesium iodide or vinyl lithium under various conditions did not give the desired vinyl alcohol **6a**. This result was unexpected because similar reactions using methylmagnesium iodide have yielded the tertiary 2-*C*-methylderivative**13** in excellent yield, which was transformed to **4a**.[18] Thus we abandoned this route and pursued the more promising route B using the sulfur ylide, as shown in Scheme 3.

Treatment of ketone **7** with trimethylsulfoxonium iodide and LiHMDS yielded epoxide **14** (66%) as a single stereoisomer via the attack of the sulfur ylide from the less hindered convex side of the molecule. Cleavage of epoxide **14** with NaOAc in acetic anhydride gave the desired 2-*C*-acetoxymethyl derivative **15** in poor yield, but the use of tetra-*n*-butylammonium acetate instead of NaOAc afforded **15** in good yield. Selective removal of the TBS group of **15** in the presence of the TBDPS group was achieved using pyridinium *p*-toluenesulfonate (PPTS) to give diol **16**. The β configuration of the 2-*C*-acetoxymethyl group in **16** was confirmed by NOE experiment.



Scheme 2. Synthetic approach to the key intermediate **7a** using route A.



Scheme 3. Introduction of the 2-*C*-hydroxymethyl group using the sulfur ylide as the nucleophile (route B).

The expected NOE (4.5%) was observed at H-2′ upon irradiation of H-3.

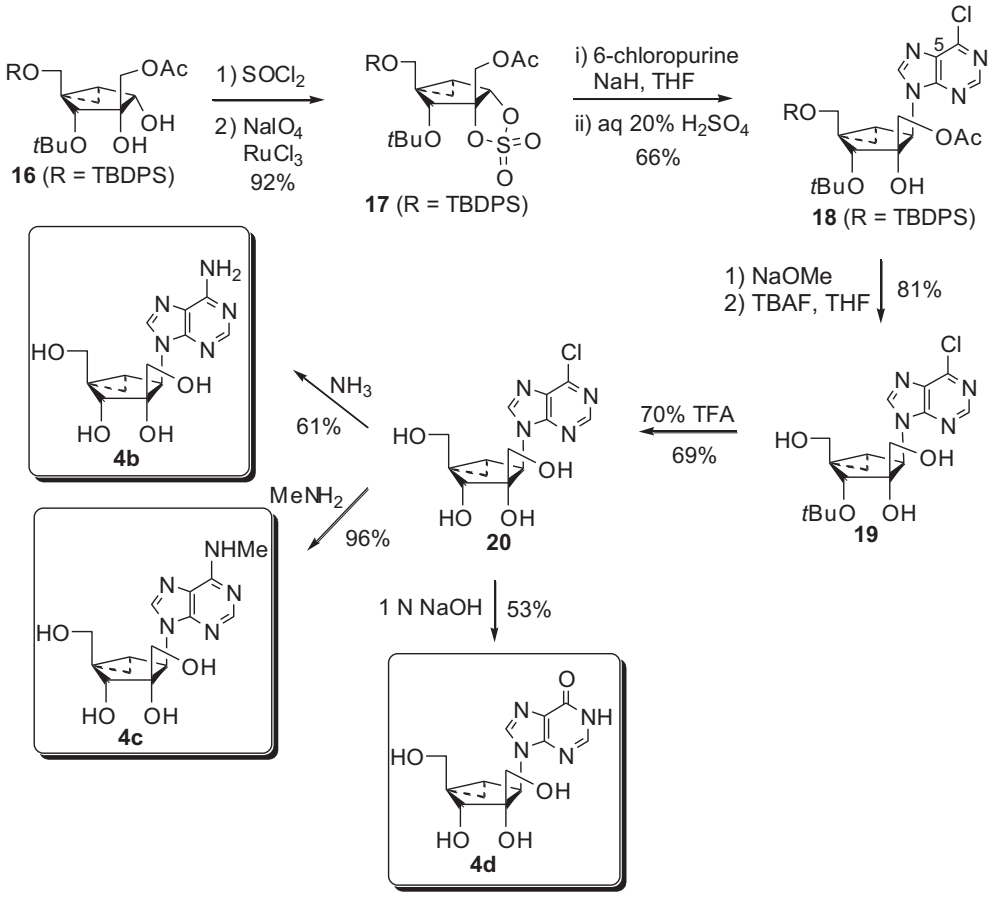
For the synthesis of the 2′-*C*-hydroxymethyl derivatives **4b**–**d**, diol **16** was converted into cyclic sulfate **17** as the glycosyl donor surrogate (Scheme 4).[24] Treatment of **16** with thionyl chloride followed by oxidation with $RuCl_3$ and $NaIO_4$, gave cyclic sulfate **17**, which was ready for condensation with purine bases. Condensation of cyclic sulfate **17** with the 6-chloropurine anion in THF gave the desired N^9-isomer **18** (66%) after hydrolysis of the resulting sulfate with aqueous sulfuric acid and without the concomitant formation of the N^7-isomer.[25]

Structural assignment of N^9-isomer **18** was accomplished by the comparison of ^{13}C NMR and UV data reported in the literature.[26,27] The N^7-and N^9-isomersare easily distinguished by the comparison of C-5 signals in their ^{13}C NMRs.[26] In general, the C-5 signal in the N^7-isomer is shifted upfield by about 10 ppm relative to the corresponding shift (~132 ppm) in the N^9-isomer. Since the C-5 signal in compound **18** appeared at 132.6 ppm, the condensed product **18** was confirmed to be the N^9-isomer. The structure of N^9-isomer **18** was also deduced from its UV spectrum, which was similar to the spectra of the N^9-isomer of 6-chloropurine reported in the literature.[27] The UV spectrum of the N^9-isomer shows absorption maxima at 265 nm, while that of the N^7-isomer shows absorption maxima at about 275 nm. The UV spectrum of **18** showed absorption maxima at 265 nm, which confirmed it is the N^9-isomer. Removal of the acetoxy group of **18** with NaOMe followed by the removal of the TBDPS group with TBAF afforded the 3′-*tert*-butyl derivative **19**. Final removal of the 3′-*tert*-butyl group with 70% trifluoroacetic acid yielded the 6-chloropurine derivative **20**. Compounds **19** and **20** also showed the same patterns of ^{13}C NMR and UV spectra of the N^9-isomer as compound **18**. Treatment of **20** with methanolic ammonia gave the adenine derivative **4b** (61%) with concomitant formation of the 6-methoxy derivative (39%). Similarly, the 6-chloropurine derivative **20** was converted into the N^6-methyladenine derivative **4c**. The hypoxanthine derivative **4d** was synthesized in 53% yield by refluxing **20** with 1 N NaOH.

The 2′-*C*-azido- and 2′-*C*-fluoromethyl-nucleosides **4e** and **4f** were also synthesized using the selective opening of the epoxide with NaN_3 and TBAF, respectively as a key step (Scheme 5). Unlike the 2-*C*-acetoxymethyl derivative, opening of epoxide **14** with NaN_3 and TBAF yielded the desired 2-*C*-azido- and 2-*C*-fluoromethyl derivatives with concomitant removal of the TBS and TBDPS groups, though in very poor yields. The poor formation of the desired compounds was attributed to the bulky protecting groups; thus, the protecting groups of **14** were first removed with TBAF to give the diol **21**. As expected, ring opening of **21** with NaN_3 and TBAF proceeded well to give the 2-*C*-azido- and 2-*C*-fluoromethyl derivatives **22** and **23**, respectively. Selective protection of the primary hydroxyl groups of **22** and **23** with TBDPS groups afforded **24** and **25**. These intermediates were converted to the 2′-*C*-azido- and 2′-*C*-fluoromethyl-substituted nucleosides **4e** and **4f** using procedures similar to those used in Scheme 4.

2.2. Anti-HCV activity

Assessment of the anti-HCV activity of **4a**–**f** was performed in a cell-based HCV replicon assay.[28] However, all synthesized compounds showed neither anti-HCV activity nor cytotoxicity up to 100 μM. This result is disappointing in that compounds **4a**–**f** adopt the same conformation as compound **3** showing potent anti-HCV activity. This result indicates that all synthesized nucleosides locked to the Northern C3′-*endo* conformation could not be converted to their triphosphates by cellular nucleoside/nucleotide



Scheme 4. Synthesis of the final 2′-*C*-hydroxymethyl nucleosides using cyclic sulfate chemistry.

kinases, because these kinases might prefer the Southern C3′-*exo* conformation and/or the HCV RNA polymerase might also prefer the Southern C3′-*exo* conformation even though the phosphorylation occurred.

3. Conclusions

In summary, we have accomplished the stereoselective synthesis of conformationally restricted 2′-*C*-substituted carbanucleosides **4a**–**f** as potential anti-HCV agents. Conformational restriction was achieved by using a bicyclo[3.1.0]hexane, and insertion of the key 2′-*C*-substituted-methyl moiety was achieved by the stereoselective conversion of the ketone into the epoxide, followed by the stereoselective opening of the epoxide with nucleophiles (OAc, N_3, or F). Other reactions, such as stereoselective cyclopropanation, regioselective cleavage of the isopropylidene group, and cyclic sulfate chemistry, were also employed for the stereoselective synthesis of the target nucleosides and are expected to be extensively used for the development of new carbasugar templates.

4. Experimental section

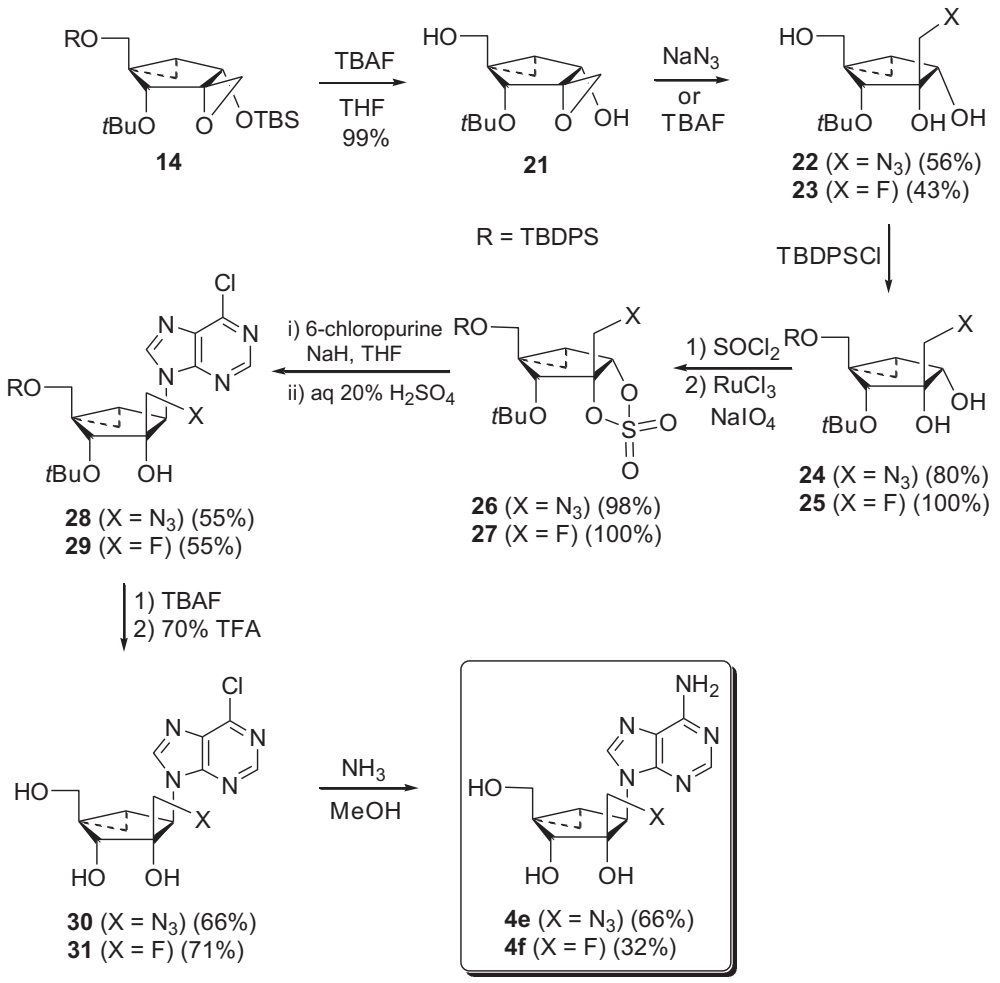
4.1. General methods

^{1}H and ^{13}C NMR spectra ($CDCl_3$ or CD_3OD) were recorded on 400 and 100 MHz NMR, respectively. The ^{1}H 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. The chemical shifts are reported as parts per million (δ) relative to the solvent peak. Column chromatography was performed on silica gel 60 (230–400 mesh). All the anhydrous solvents were distilled over CaH_2, P_2O_5 or sodium/benzophenone prior to the reaction.

4.2. Chemistry

*4.2.1. (+)-(1R,2R,3R,4S,5R)-2-tert-Butoxy-4-(tert-butyl-dimethyl-silanyloxy)-1-(tert-butyl-diphenyl-silanyloxymethyl)-bicyclo[3.1.0]hexan-3-ol (**12**).* To a stirred solution of **11**[16] (21.94 g, 48.25 mmol) in methylene chloride (210 mL), imidazole (13.14 g, 193.0 mmol) and *tert*-butyldimethylsilyl chloride (14.55 g, 96.51 mmol) were added at 0 °C and the reaction mixture was stirred at rt overnight. The mixture was partitioned between methylene chloride and water, and the organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=50/1) to give **12** (23.71 g, 86%) as a colourless syrup: ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.25 (m, 1H), 0.91 (s, 9H), 1.06 (s, 9H), 1.10 (m, 1H), 1.24 (s, 9H), 1.38 (t, J=4.8 Hz, 1H), 3.02 (d, J=11.2 Hz, 1H), 3.76 (m, 1H), 4.17 (d, J=11.2 Hz, 1H), 4.32 (m, 1H), 4.39 (d, J=6.0 Hz, 1H), 7.26–7.43 (m, 6H), 7.61–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.6, −4.2, −3.4, 10.0, 18.5, 19.5, 25.9, 26.1, 27.0, 27.2, 28.6, 35.4, 65.6, 71.4, 72.3, 72.9, 73.7, 127.86, 127.91, 129.9, 135.8; $[\alpha]_D^{19.9}$ +47.7 (*c* 1.12, MeOH); IR (neat) 3557.32, 1471.78, 1362.45 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{33}H_{52}NaO_4Si_2$ $[M+Na]^+$: 591.3302; found: 591.3304.

*4.2.2. (+)-(1R,2R,4S,5R)-2-tert-Butoxy-4-(tert-butyl-dimethyl-silanyloxy)-1-(tert-butyl-diphenyl-silanyloxymethyl)-bicyclo[3.1.0]hexan-3-one (**7**).* Dimethyl sulfoxide (5.9 mL, 83.53 mmol) was



Scheme 5. Synthesis of the final 2′-*C*-azido- and 2′-*C*-fluoromethyl nucleosides using cyclic sulfate chemistry.

added slowly to the solution of oxalyl chloride (20.9 mL, 41.76 mmol, 2.0 M solution in dichloromethane) in methylene chloride (50 mL) at −78 °C and the reaction mixture was stirred at −78 °C for 30 min. To this reaction mixture was added a solution of alcohol **12** (7.92 g, 13.92 mmol) in methylene chloride (50 mL) at −78 °C and the reaction mixture was stirred for 1 h at the same temperature. After triethylamine (23.3 mL, 167.0 mmol) was added to the mixture at −78 °C, the reaction mixture was further stirred at rt for 1 h. After adding saturated aqueous NH_4Cl solution carefully at 0 °C, the reaction mixture was partitioned between methylene chloride and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=50/1) to give **7** (7.5 g, 95%) as a white solid: mp 107.2–109.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.56 (s, 3H), 0.11 (s, 3H), 0.45 (m, 1H), 0.64 (m, 1H), 0.89 (s, 9H), 1.09 (s, 9H), 1.26(s, 9H), 1.29 (m, 1H), 3.06 (d, *J*=11.2 Hz, 1H), 4.29 (d, *J*=11.2 Hz, 1H), 4.56 (dt, *J*=6.0 Hz, 1H), 4.82 (s, 1H), 7.38–7.46 (m, 6H), 7.64–7.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.6, −4.3, 9.4, 18.6, 19.5, 23.8, 26.0, 27.2, 28.6, 30.4, 64.8, 73.2, 74.6, 74.7, 77.4, 128.0, 130.1, 130.2, 133.5, 134.0, 135.9, 212.1; $[\alpha]_D^{26.7}$ +59.7 (*c* 1.09, MeOH); IR (neat) 2360.02, 1772.67, 1471.99, 1363.84 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{33}H_{50}NaO_4Si_2$ $[M+Na]^+$: 589.3145; found: 589.3151.

*4.2.3. (+)-(1R,2R,3R,4S,5R)-2-tert-Butoxy-1-(hydroxymethyl)spiro[bicyclo[3.1.0]hexane-3,2′-oxiran]-4-ol (**14**).* Lithium bis-(trimethylsilyl) amide (2.82 mL, 2.82 mmol, 1.0 M solution in tetrahydrofuran) was slowly added to the suspension of trimethylsulfoxonium iodide (0.56 g, 2.54 mmol) in tetrahydrofuran (5 mL) at 0 °C, and the reaction mixture was stirred at rt for 1.5 h. To this reaction mixture was added a solution of **7** (622.7 mg, 1.10 mmol) in tetrahydrofuran (5 mL) at 0 °C, and the reaction mixture was stirred at rt for 5 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=30/1) to give **14** (419 mg, 66%) as a white solid: mp 124.0–127.6 °C; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.25 (m, 1H), 0.86 (s, 9H), 1.02 (m, 1H), 1.09 (s, 9H), 1.19 (m, 1H), 1.23 (s, 9H), 2.43 (d, *J*=5.6 Hz, 1H), 2.57 (d, *J*=5.6 Hz, 1H), 4.28 (d, *J*=11.6 Hz, 1H), 4.28 (d, *J*=11.2 Hz, 1H), 4.46 (d, *J*=4.4 Hz, 1H), 4.62 (s, 1H), 7.36–7.46 (m, 6H), 7.62–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.2, −3.9, 9.4, 18.5, 19.52, 26.1, 26.3, 27.2, 29.1, 33.4, 40.9, 60.0, 65.0, 67.5, 69.7, 73.6, 127.9, 130.0, 130.1, 133.8, 134.0, 135.8, 135.9; $[\alpha]_D^{19.9}$ +60.7 (*c* 1.12, MeOH); IR (neat) 2928.37, 1737.90, 1470.89, 1363.27, 1112.32 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{34}H_{52}NaO_4Si_2$ $[M+Na]^+$: 603.3296; found: 603.3304. Anal. Calcd for $C_{34}H_{52}O_4Si_2$: C, 70.29; H, 9.02. Found: C, 70.54; H, 9.35.

*4.2.4. (+)-(1R,2R,3R,4S,5R)-Acetic acid 2-tert-butoxy-4-(tert-butyl-dimethyl-silanyloxy)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-hydroxy-bicyclo[3.1.0]hex-3-ylmethyl ester (**15**).* To a stirred suspension of **14** (1.11 g, 1.91 mmol) in acetic anhydride (15 mL) was added tetra-*n*-butylammonium acetate (2.30 g, 7.64 mmol) at rt, and the reaction mixture was stirred at 100 °C for 2 days. The reaction mixture was partitioned between ethyl acetate and water.

The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=20/1) to give **15** (605 mg, 49%) as a colourless syrup: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, CH_3, 3H), 0.07 (s, CH_3, 3H), 0.23 (m, 1H), 0.89 (s, 9H), 1.07 (s, 9H), 1.17 (m, 1H), 1.22 (s, 9H), 1.44 (t, *J*=4.8 Hz, 1H), 2.05 (s, 3H), 2.94 (d, *J*=11.2 Hz, 1H), 3.18 (br s, 1H), 3.92 (d, *J*=11.2 Hz, 1H), 4.06 (d, *J*=11.2 Hz, 1H), 4.15 (d, *J*=11.2 Hz, 1H), 4.16 (s, 1H), 4.39 (s, 1H), 7.36–7.44 (m, 6H), 7.63–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −4.7, −4.3, 10.0, 18.4, 19.4, 21.1, 26.0, 27.1, 28.4, 29.0, 35.5, 65.2, 66.2, 71.1, 72.8, 73.9, 78.1, 127.9, 130.00, 130.02, 133.6, 133.7, 135.8, 135.9, 170.9; $[\alpha]_D^{21.0}$ +36.2 (*c* 0.47, MeOH); IR (neat) 3454.45, 2931.502, 1745.63, 1366.54, 1037.84 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{36}H_{56}NaO_6Si_2$ $[M+Na]^+$: 663.3508; found: 663.3526.

*4.2.5. (+)-(1R,2R,3S,4S,5R)-Acetic acid 2-tert-butoxy-1-(tert-butyl-diphenyl-silanyloxymethyl)-3,4-dihydroxy bicyclo[3.1.0]hex-3-ylmethyl ester (**16**).* To a solution of **15** (69.5 mg, 0.108 mmol) in ethanol (8 mL) was added pyridinium *p*-toluenesulfonic acid (10.9 mg, 0.043 mmol) at rt, and the reaction mixture was stirred at 55 °C for 2 days. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=4/1) to give **16** (47.3 mg, 83%) as a colourless syrup: ^{1}H NMR ($CDCl_3$) δ 0.17 (m, 1H), 1.08 (s, 9H), 1.13 (t, *J*=4.8 Hz, 1H), 1.27 (m, 1H), 1.28 (s, 9H), 2.03 (s, 3H), 2.92 (d, *J*=11.2 Hz, 1H), 3.49 (br s, 1H), 3.86 (d, *J*=11.2 Hz, 1H), 3.95 (d, *J*=11.2 Hz, 1H), 4.17 (d, *J*=11.6 Hz, 1H), 4.21 (d, *J*=5.2 Hz, 1H), 4.66 (s, 1H), 7.36–7.46 (m, 6H), 7.62–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 8.5, 19.5, 21.0, 27.1, 29.1, 29.5, 35.0, 64.9, 65.4, 70.3, 72.2, 75.0, 75.2, 128.0, 130.1, 130.2, 133.5, 133.6, 135.79, 135.81, 170.8; $[\alpha]_D^{23.5}$ +29.9 (*c* 1.43, MeOH); IR (neat) 3458.23, 1746.15, 1471.06, 1366.55 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{30}H_{42}NaO_6Si$ $[M+Na]^+$: 549.2650; found: 549.2646.

*4.2.6. (1S,4aR,5R,5aR,6R)-Acetic acid 5-tert-butoxy-5a-(tert-butyl-diphenyl-silanyloxymethyl)-3,3-dioxo-tetrahydro-2,4-dioxa-3λ^6-thia-cyclopropa[a]pentalen-4a-ylmethyl ester (**17**).* To a solution of **16** (315 mg, 0.598 mmol) in methylene chloride (4 mL) were added triethylamine (0.3 mL, 2.09 mmol) and thionyl chloride (0.07 mL, 0.897 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 10 min. The reaction mixture was partitioned between methylene chloride and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=10/1) to give cyclic sulfite (316 mg, 92%) as a diastereomeric mixture, colourless syrup; ^{1}H NMR ($CDCl_3$) δ 0.56 (m, 1.6H), 0.61 (m, 1H), 1.08 (s, 22.7H), 1.17 (s, 14.2H), 1.22 (s, 9H), 1.33 (m, 1.8H), 1.43–1.48 (m, 1.8H), 1.79 (m, 1H), 2.95 (d, *J*=11.6 Hz, 1H), 3.01 (d, *J*=11.6 Hz, 1.7H), 4.08 (dd, *J*=1.2, 11.6 Hz, 3H), 4.11–4.17 (m, 2.3H), 4.31 (d, *J*=8.8 Hz, 2.2H), 4.34 (d, *J*=7.6 Hz, 1H), 4.38 (s, 1H), 4.46 (s, 1H), 4.55 (d, *J*=12.4 Hz, 1H), 5.11 (d, *J*=5.6 Hz, 1H), 5.32 (dd, *J*=0.8, 4.8 Hz, 1.6H), 7.37–7.41 (m, 10H), 7.43–7.47 (m, 5H), 7.60–7.63 (m, 6H), 7.63–7.66 (m, 4H); IR (neat) 1754.52, 1427.52, 1390.05, 1203.56 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{30}H_{40}NaO_7SSi$ $[M+Na]^+$: 595.2156; found: 595.2169.

To a solution of cyclic sulfite (228 mg, 0.398 mmol) in carbon tetrachloride, acetonitrile and water (1/1/1.5, 3.5 mL) were added sodium periodate (237 mg, 0.756 mmol) and ruthenium chloride trihydrate (23 mg), and the reaction mixture was stirred at rt for 10 min. The reaction mixture was partitioned between methylene chloride and water and the organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=6/1) to give **17** (228 mg) as a colourless syrup, which was immediately used for the next reaction.

*4.2.7. (+)-(1R,2R,3R,4R,5R)-(Acetic acid 2-tert-butoxy-1-(tert-butyl-diphenyl-silanyloxymethyl)-4-(6-chloro-purin-9-yl)-3-hydroxy-bicyclo[3.1.0]hex-3-ylmethyl ester (**18**).* A suspension of 6-chloropurine (154 mg, 0.996 mmol), sodium hydride (43 mg, 1.075 mmol, 60% dispersion in mineral oil) and 18-crown-6 (284 mg, 1.075 mmol) in tetrahydrofuran (5 mL) was stirred at 80 °C. To this reaction mixture, a solution of **17** (228 mg, 0.398 mmol) in tetrahydrofuran (5 mL) was added, and stirring was continued at 80 °C overnight. The reaction mixture was cooled to 0 °C, and 20% sulfuric acid was added slowly until a pH of 1–2 was attained. Subsequently, the reaction mixture was stirred at rt for an additional 1 h, then neutralized with 1 N NaOH solution until a pH of 6 was attained. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate=3/1) to give **18** (173 mg, 66%) as a colourless syrup: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 0.68 (m, 1H), 1.15 (s, 9H), 1.22 (s, 9H), 1.26 (m, 1H), 1.57(m, 1H), 1.68 (s, 3H), 3.29 (d, *J*=11.2 Hz, 1H), 3.44 (d, *J*=12.4 Hz, 1H), 3.86 (d, *J*=12.4 Hz, 1H), 4.22 (d, *J*=11.2 Hz, 1H), 4.85 (s, 1H), 5.17 (s, 1H), 7.35–7.46 (m, 6H), 7.61–7.68 (m, 4H), 8.72 (s, 1H), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.8, 19.4, 20.2, 25.3, 27.5, 29.1, 36.2, 62.0, 65.0, 65.5, 70.2, 75.6, 80.6, 128.0, 128.2, 130.3, 130.4, 131.6, 132.6, 132.8, 135.7, 136.1, 145.5, 151.1, 152.2, 152.4, 169.5; $[\alpha]_D^{20.2}$ +21.6 (*c* 1.53, MeOH); IR (neat) 3465.47, 2963.51, 2931.79, 1747.86, 1590.31, 1427.85 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{35}H_{43}ClN_4NaO_5Si$ $[M+Na]^+$: 685.2583; found: 685.2569.

*4.2.8. (+)-(1R,2R,3R,4R,5R)-2-tert-Butoxy-4-(6-chloro-purin-9-yl)-1,3-bis-hydroxymethyl-bicyclo[3.1.0]hexan-3-ol (**19**).* To a solution of **18** (167 mg, 0.252 mmol) in methanol (2 mL) was added sodium methoxide (13.6 mg, 0.252 mmol), and the reaction mixture was stirred at rt for 6 h. After evaporation, the residue was dissolved in tetrahydrofuran (2 mL). To this solution, tetra-*n*-butylammonium fluoride (0.38 mL, 0.378 mmol, 1.0 M solution in tetrahydrofuran) was added, and the reaction mixture was stirred at rt for 1 h. After the solvent was evaporated, the residue was purified by silica gel column chromatography (methylene chloride/methanol=30/1) to give**19** (78.5 mg, 81%) as a white solid: mp 208.9–213.4 °C; UV (MeOH) λ_{max} 265 nm; ^{1}H NMR (CD_3OD) δ 0.73 (m, 1H), 1.31 (s, 9H), 1.47 (m, 1H), 1.60 (m, 1H), 2.76 (d, *J*=11.6 Hz, 1H), 3.17 (d, *J*=12.0 Hz, 1H), 3.35 (d, *J*=12.0 Hz, 1H), 4.25 (d, *J*=12.0 Hz, 1H), 4.68 (s, 1H), 4.93 (s, 1H), 8.32 (s, 1H), 8.72 (s, 1H); ^{13}C NMR (CD_3OD) δ 12.8, 26.2, 29.5, 37.4, 64.4, 64.87, 64.94, 71.1, 76.2, 82.7, 132.4, 149.3, 151.0, 152.7, 153.9; $[\alpha]_D^{23.7}$ +38.5 (*c* 1.12, MeOH); IR (neat) 3387.87, 1593.60, 1563.14, 1198.47, 1057.57 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{17}H_{23}Cl_2N_4O_4$ $[M+Cl]^-$: 417.1102; found: 417.1107.

*4.2.9. (−)-(1R,2R,3R,4R,5R)-4-(6-Chloro-purin-9-yl)-1,3-bis-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**20**).* A solution of **19** (17 mg, 0.044 mmol) in 70% aqueous trifluoroacetic acid (2 mL) was stirred at rt for 1 h, and the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol=10/1) to give **20** (10 mg, 69%) as a white solid: mp 215.3–223.2 °C (decomp.); UV (MeOH) λ_{max} 265 nm; ^{1}H NMR (CD_3OD) δ 0.76 (m, 1H), 1.61 (m, 1H), 1.77 (m, 1H), 2.74 (d, *J*=11.2 Hz, 1H), 3.18 (d, *J*=11.6 Hz, 1H), 3.35 (d, *J*=11.6 Hz, 1H), 4.32 (d, *J*=11.2 Hz, 1H), 4.73 (s, 1H), 5.14 (s, 1H), 8.72 (s, 1H), 8.98 (s, 1H); ^{13}C NMR (CD_3OD) δ 12.6, 25.0, 38.0, 64.2, 64.8, 65.5, 72.8, 82.3, 132.4, 148.6, 151.3, 152.8, 153.6; $[\alpha]_D^{23.5}$ −34.5 (*c* 0.85, MeOH); IR (neat) 3349.96, 2107.69, 1678.64, 1594.12, 1567.44, 1202.28 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{13}H_{16}ClN_4O_4$ $[M+H]^+$: 327.0855; found: 327.0858.

*4.2.10. (−)-(1R,2R,3R,4R,5R)-4-(6-Amino-purin-9-yl)-1,3-bis-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**4b**).* A mixture of **20** (61 mg, 0.187 mmol) and saturated methanolic ammonia (2 mL)

was stirred at 80 °C overnight, and the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol=5/1) to give **4b** (35 mg, 61%) as a white solid after recrystallisation from methanol: mp 210.7–220.4 °C(decomp.); UV (MeOH) λ_{max} 260 nm; ^{1}H NMR (CD_3OD) δ 0.72 (m, 1H), 1.61 (m, 1H), 1.71(t, J=11.6 Hz, 1H), 2.88 (d, J=11.6 Hz, 1H), 3.14 (d, J=11.2 Hz, 1H), 3.29 (d, J=11.6 Hz, 1H), 4.30 (d, J=11.2 Hz, 1H), 4.64 (s, 1H), 4.95 (s, 1H), 8.17 (s, 1H), 8.41 (s, 1H); ^{13}C NMR (CD_3OD) δ 11.5, 23.5, 36.4, 61.5, 62.7, 64.2, 70.9, 80.4, 118.5, 140.6, 149.6, 152.2, 155.9; $[\alpha]_D^{21.9}$ −30.5 (*c* 1.78, MeOH); IR (neat) 3444.42, 1681.81, 1440.96, 1208.15, 1140.29 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{13}H_{18}N_5O_4$ $[M+H]^+$: 308.1353; found: 308.1355. Anal. Calcd for $C_{13}H_{17}N_5O_4$: C, 50.81; H, 5.58; N, 22.79. Found: C, 50.55; H, 5.90; N, 22.50.

4.2.11. (−)-(1R,2R,3R,4R,5R)-1,3-Bis-hydroxymethyl-4-(6-methoxy-purin-9-yl)-bicyclo[3.1.0]hexane-2,3-diol (N^6-OMe derivative). UV (MeOH) λ_{max} 250 nm; ^{1}H NMR (CD_3OD) δ 0.72–0.76 (m, 1H), 1.61 (m, 1H), 1.74 (t, J=4.0 Hz, 1H), 2.87 (d, J=11.2 Hz, 1H), 3.14 (d, J=11.2 Hz, 1H), 3.31 (m, 1H), 4.18 (s, OCH_3, 3H), 4.31 (d, J=11.2 Hz, 1H), 5.05 (s, 1H), 8.49 (s, 1H), 8.64 (s, 1H); ^{13}C NMR (CD_3OD) δ 12.6, 15.6, 25.1, 38.0, 55.0, 64.5, 65.0, 65.9, 67.1, 73.2, 82.4, 122.2, 145.3, 153.0, 153.3, 162.55, 162.61; IR (neat) 3367.09, 1681.33, 1605.14, 1204.22 cm^{-1}.

*4.2.12. (−)-(1R,2R,3R,4R,5R)-1,3-Bis-hydroxymethyl-4-(6-methylamino-purin-9-yl)-bicyclo[3.1.0]hexane-2,3-diol (**4c**).* A solution of **20** (43.6 mg, 0.133 mmol) and 40% aqueous methylamine (2 mL) was heated at 80 °C overnight, and the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol=5/1) to give **4c** (42.1 mg, 98%) as a white solid after recrystallisation from methanol: mp 117.3–124.5 °C; UV (MeOH) λ_{max} 268 nm; ^{1}H NMR (CD_3OD) δ 0.72 (m, 1H), 1.61 (m, 1H), 1.70 (t, J=4.8 Hz, 1H), 2.87 (d, J=11.6 Hz, 1H), 3.13 (d, J=11.2 Hz, 1H), 3.28 (d, J=11.6 Hz, 1H), 4.31 (d, J=11.2 Hz, 1H), 4.64 (s, 1H), 4.94 (s, 1H), 8.22 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (CD_3OD) δ 12.6, 25.2, 30.9, 38.0, 64.7, 65.2, 66.1, 73.4, 82.5, 119.7, 142.9, 149.7, 153.5, 157.1; $[\alpha]_D^{21.5}$ −26.0 (*c* 0.73, MeOH); IR (neat) 3368.44, 1678.68, 1631.45, 1205.92, 1140.77 cm^{-1};HR-ESIMS (*m*/*z*) calcd for $C_{14}H_{20}N_5O_4$ $[M+H]^+$: 322.1510; found: 322.1513. Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.79. Found: C, 52.85; H, 5.91; N, 21.51.

*4.2.13. (−)-(1R,2R,3R,4R,5R)-9-(3,4-Dihydroxy-3,5-bis-hydroxymethyl-bicyclo[3.1.0]hex-2-yl)-1,9-dihydro-purin-6-one (**4d**).* A solution of **20** (79.5 mg, 0.243 mmol) in 1 N NaOH solution (2 mL) was heated at 100 °C for 10 min, and the reaction mixture was evaporated. The residue was purified by reverse silica gel column chromatography (0–3%acetone in water) to give **4d** (39.8 mg, 53%) as a white solid after recrystallisation from methanol: mp 104.5–116.4 °C; UV (MeOH) λ_{max} 250 nm; ^{1}H NMR (CD_3OD) δ 0.72 (m, 1H), 1.56 (m, 1H), 1.72 (t, J=4.8 Hz, 1H), 2.95 (d, J=11.6 Hz, 1H), 3.15 (d, J=11.2 Hz, 1H), 3.31 (d, J=11.2 Hz, 1H), 4.28 (d, J=11.2 Hz, 1H), 4.62 (s, 1H), 4.99 (s, 1H), 8.04 (s, 1H), 8.49 (s, 1H); ^{13}C NMR (CD_3OD) δ 12.5, 25.3, 38.0, 63.7, 64.7, 65.9, 73.3, 82.3, 125.1, 142.1, 146.6, 150.4, 159.2; $[\alpha]_D^{22.3}$ −60.3 (*c* 1.56, MeOH); IR (neat) 3376.81, 1693.85, 1588.00, 1414.25, 1214.11, 1071.85 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{13}H_{17}N_4O_5$ $[M+H]^+$: 309.1193; found: 309.1191. Anal. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.65; H, 5.23; N, 18.17. Found: C, 50.64; H, 5.40; N, 18.51.

*4.2.14. (+)-(1R,2R,3S,4S,5R)-2-tert-Butoxy-1-(hydroxymethyl)spiro[bicyclo[3.1.0]hexane-3,2′-oxiran]-4-ol (**21**).* To a solution of **14** (215.5 mg, 0.371 mmol) in tetrahydrofuran (3 mL) was dropwise added tetra-*n*-butylammonium fluoride (0.93 mL, 0.927 mmol, 1.0 M solution in tetrahydrofuran) at 0 °C, and the reaction mixture was stirred at rt for 3 h. After evaporation, the residue was purified by silica gel column chromatography (methylene chloride/methanol=20/1) to give diol **21** (83.8 mg, 99%) as colourless syrup: ^{1}H NMR (CD_3OD) δ 0.47 (m, 1H), 1.10 (m, 1H), 1.23 (s, 9H), 1.57 (m, 1H), 2.54 (d, J=4.4 Hz, 1H), 2.68 (d, J=4.8 Hz, 1H), 3.07 (d, J=11.6 Hz, 1H), 4.07 (d, J=11.6 Hz, 1H), 4.41 (d, J=4.4 Hz, 1H), 4.66 (s, 1H); ^{13}C NMR (CD_3OD) δ 9.6, 26.7, 29.3, 34.1, 42.3, 61.6, 64.1, 69.2, 69.7, 75.4; $[\alpha]_D^{21.7}$ +39.2 (*c* 1.39, MeOH); IR (neat) 3419.13, 1737.28, 1367.28, 1071.34 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{12}H_{20}NaO_4$ $[M+Na]^+$: 251.1254; found: 251.1261.

*4.2.15. (+)-(1R,2S,3S,4R,5R)-3-Azidomethyl-4-tert-butoxy-5-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**22**).* To a solution of **21** (47.6 mg, 0.209 mmol) in *N*,*N*-dimethylformamide (2 mL) was added sodium azide (20.3 mg, 0.313 mmol) at 0 °C, and the reaction mixture was stirred at rt for 2 d. After evaporation, the residue was purified by silica gel column chromatography (methylene chloride/methanol=20/1) to give **22** (56.5 mg, 56%) as a colourless syrup: ^{1}H NMR (CD_3OD) δ 0.38 (m, 1H), 1.30 (s, 9H), 1.39 (t, J=4.8 Hz, 1H), 1.53 (m, 1H), 2.98 (d, J=11.6 Hz, 1H), 3.21 (d, J=12.4 Hz, 1H), 3.32 (d, J=12.8 Hz, 1H), 4.02 (d, J=11.6 Hz, 1H), 4.10 (d, J=5.6 Hz, 1H), 4.37 (s, 1H); ^{13}C NMR (CD_3OD) δ 10.2, 28.8, 29.5, 36.0, 56.5, 65.1, 72.9, 74.0, 75.7, 79.4; $[\alpha]_D^{20.7}$ +24.7 (*c* 1.27, MeOH); IR (neat) 2110.26 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{12}H_{21}N_3NaO_4$ $[M+Na]^+$: 294.1424; found: 294.1426. Anal. Calcd for $C_{12}H_{21}N_3O_4$: C, 53.12; H, 7.80; N, 15.49. Found: C, 53.13; H, 7.98; N, 15.50.

*4.2.16. (+)-(1R,2S,3R,4R,5R)-4-tert-Butoxy-3-fluoromethyl-5-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**23**).* To a solution of **21** (124.0 mg, 0.543 mmol) in tetrahydrofuran (10 mL) was added tetra-*n*-butylammonium fluoride (2.71 mmol, dried under pump prior to the reaction) in tetrahydrofuran (2 mL) at 0 °C, and the reaction mixture was stirred at 60 °C overnight. After evaporation, the residue was purified by silica gel column chromatography (methylene chloride/methanol=50/1) to give **23** (58.5 mg, 43%) as colourless syrup: ^{1}H NMR (CD_3OD) δ 0.35 (dd, J=5.2, 8.4 Hz, 1H), 1.29 (s, 9H), 1.42 (t, J=4.8 Hz, 1H), 1.53 (m, 1H), 2.98 (d, J=12.0 Hz, 1H), 4.03 (d, J=12.0 Hz, 1H), 4.05 (dd, J=9.6, 25.6 Hz, 1H), 4.17 (dd, J=9.6, 25.6 Hz, 1H), 4.22 (m, 1H), 4.50 (s, 1H); ^{19}F NMR (CD_3OD) δ −228.85 (td, J=1.1, 47.8 Hz); ^{13}C NMR (CD_3OD) δ 9.9, 28.4, 29.3, 35.3, 64.8, 70.9, 72.4, 75.6, 76.4 (J=18.4 Hz), 81.9, 83.7; $[\alpha]_D^{20.7}$ +28.2 (*c* 0.85, MeOH); IR (neat) 3427.05, 1367.85, 1187.55, 1070.02, 1021.24 cm^{-1}. Anal. Calcd for $C_{12}H_{21}FO_4$: C, 58.05; H, 8.52. Found: C, 58.13; H, 8.88.

*4.2.17. (+)-(1R,2S,3S,4R,5R)-3-Azidomethyl-4-tert-butoxy-5-(tert-butyl-diphenyl-silanyloxymethyl)-bicyclo[3.1.0]hexane-2,3-diol (**24**).* To a solution of **22** (56.5 mg, 0.208 mmol) in dimethylformamide (3 mL) were added imidazole (42.5 mg, 0.624 mmol) and *tert*-butylchlorodiphenylsilane (0.08 mL, 0.312 mmol) at 0 °C, and the reaction mixture was stirred at rt for 5 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by silica gel column chromatography (hexane/ethylacetate=10/1) to give **24** (85.0 mg, 80%) as a colourless syrup: ^{1}H NMR ($CDCl_3$) δ 0.21 (m, 1H), 1.09 (s, 9H), 1.22 (m, 1H), 1.28 (s, 9H), 2.48 (d, J=8.4 Hz, 1H), 2.94 (d, J=11.2 Hz, 1H), 3.18 (d, J=12.4 Hz, 1H), 3.36 (d, J=12.4 Hz, 1H), 3.62 (s, 1H), 4.10 (m, 1H), 4.15 (d, J=11.2 Hz, 1H), 4.57 (s, 1H), 7.37–7.44 (m, 6H), 7.63–7.66 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 8.6, 19.4, 27.1, 29.1, 29.3, 35.3, 55.3, 65.4, 71.1, 73.0, 75.1, 77.3, 128.0, 130.0, 130.2, 133.6, 135.8, 135.9; $[\alpha]_D^{20.8}$ +53.6 (*c* 1.85, MeOH); IR (neat) 2104.75 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for-$C_{28}H_{39}N_3NaO_4Si$ $[M+Na]^+$: 532.2602; found: 532.2609.

4.2.18. (+)-(1R,2S,3R,4R,5R)-4-tert-Butoxy-5-(tert-butyl-diphenyl-silanyloxymethyl)-3-fluoromethyl-bicyclo[3.1.0]hexane-2,3-diol

(***25***). Using the similar procedure used in the preparation of **24**, compound **23** (25.6 mg, 0.103 mmol) was converted to **25** (50.0 mg, 100%) as a colourless syrup: ^{1}H NMR ($CDCl_3$) δ 0.19 (m, 1H), 1.07 (m, 1H), 1.08 (s, 9H), 1.20 (m, 1H), 1.30 (s, 9H), 2.47 (d, J=9.6 Hz, 1H), 2.95 (d, J=11.6 Hz, 1H), 3.44 (s, 1H), 4.06 (dd, J=9.2, 48.0 Hz, 1H), 4.19 (d, J=11.6 Hz, 1H), 4.22 (dd, J=9.2, 48.0 Hz, 1H), 4.22 (m, 1H), 4.73 (s, 1H), 7.36–7.46 (m, 6H), 7.62–7.65 (m, 4H); ^{19}F NMR (CD_3OD) δ −227.88 (d, J=47.4 Hz); ^{13}C NMR ($CDCl_3$) δ 8.3, 19.4, 27.1, 29.1, 29.3, 35.1, 65.1, 69.6 (J=2.9 Hz), 71.7, 75.0 (J=16.8 Hz), 80.9, 82.7, 127.9 (J=2.2 Hz), 130.0 (J=17.5 Hz), 133.7 (J=4.4 Hz), 135.8 (J=8.0 Hz); $[\alpha]_D^{20.8}$ +23.8 (*c* 1.17, MeOH); IR (neat) 3453.32, 1471.45, 1427.93, 1112.84, 1060.59, 702.12 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{28}H_{39}FKO_4Si$ $[M+K]^+$: 525.2233; found: 525.2227.

*4.2.19. (1S,4aR,5R,5aR,6R)-(4a-Azidomethyl-5-tert-butoxy-3,3-dioxo-tetrahydro-2,4-dioxa-3λ^6-thia-cyclopropa[a]pentalen-5a-yl-methoxy)-tert-butyl-diphenyl-silane (**26**).* Using the similar procedure used in the preparation of **17**, compound **24** (85 mg, 0.167 mmol) was converted to cyclic sulfite (91 mg, 98%) as a colourless syrup: ^{1}H NMR ($CDCl_3$) δ 0.55 (m, 1H), 1.09 (s, 11.8H), 1.17 (s, 8.2H), 1.22 (s, 4H), 1.36 (m, 2H), 1.76 (m, 0.5H), 2.94 (d, J=10.4 Hz, 0.5H), 2.97 (d, J=11.6 Hz, 1H), 3.32 (d, J=13.2 Hz, 0.5H), 3.66 (d, J=13.2 Hz, 0.5H), 3.72 (d, J=13.2 Hz, 1H), 3.79 (d, J=13.2 Hz, 1H), 4.11 (d, J=11.6 Hz, 1H), 4.14 (d, J=8.4 Hz, 0.5H), 4.35 (d, J=14.4 Hz, 1.4H), 5.16 (d, J=9.2 Hz, 0.5H), 5.27 (dd, J=1.2, 4.4 Hz, 1H), 7.38–7.48 (m, 7.5H), 7.60–7.66 (m, 5H); IR (neat) 1391.39, 1214.41, 1105.21, 702.80 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{28}H_{37}N_3NaO_5SSi$ $[M+Na]^+$: 578.2115; found: 578.2127.

Using the similar procedure used in the preparation of **17**, cyclic sulfite (315.9 mg, 0.552 mmol) was converted to **26** (315.9 mg) as a colourless syrup, which was immediately used for the next reaction.

*4.2.20. (1S,4aR,5R,5aR,6R)-(5-tert-Butoxy-4a-fluoromethyl-3,3-dioxo-tetrahydro-2,4-dioxa-3λ^6-thia-cyclopropa[a]pentalen-5a-yl-methoxy)-tert-butyl-diphenyl-silane (**27**).* Using the similar procedure used in the preparation of **26**, compound **25** (58.6 mg, 0.120 mmol) was converted to cyclic sulfite (65.0 mg, 100%) as a diastereomeric mixture, a colourless syrup: major: ^{1}H NMR ($CDCl_3$) δ 0.53 (m, 1H), 1.08 (s, 9H), 1.21 (s, 9H), 1.23 (m, 1H), 1.29 (m, 1H), 2.98 (d, J=11.6 Hz, 1H), 4.14 (d, J=11.6 Hz, 1H), 4.48 (dd, J=10.0, 48.0 Hz, 1H), 4.59 (s, 1H), 4.73 (dd, J=10.0, 47.2 Hz, 1H), 5.35 (d, J=5.6 Hz, 1H), 7.32–7.44 (m, 6H), 7.61–7.65 (m, 4H); ^{19}F NMR (CD_3OD) δ −223.10 (d, J=47.0 Hz). minor: ^{1}H NMR ($CDCl_3$) δ 0.63 (m, 1H), 1.08 (s, 9H), 1.21 (s, 9H), 1.23 (m, 1H), 1.80 (dd, J=4.4, 6.0 Hz, 1H), 2.96 (d, J=11.6 Hz, 1H), 4.16 (d, J=11.6 Hz, 1H), 4.34 (dd, J=10.0, 46.4 Hz, 1H), 4.44 (s, 1H), 4.63 (dd, J=10.0, 46.8 Hz, 1H), 5.24 (d, J=5.2 Hz, 1H), 7.32–7.44 (m, 6H), 7.61–7.65 (m, 4H); ^{19}F NMR (CD_3OD) δ −225.67 (d, J=47.2 Hz).

Using the similar procedure used in the preparation of **26**, cyclic sulfite (65.0 mg, 0.122 mmol) was converted to **27** (65.1 mg) as a colourless syrup, which was immediately used for the next reaction.

*4.2.21. (−)-(1R,2R,3R,4R,5R)-3-Azidomethyl-2-tert-butoxy-1-(tert-butyl-diphenyl-silanyloxymethyl)-4-(6-chloro-purin-9-yl)-bicyclo[3.1.0]hexan-3-ol (**28**).* Using the similar procedure used in the preparation of **18**, compound **26** (315.9 mg, 0.552 mmol) was converted to **28** (200.3 mg, 55%) as a colourless syrup: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 0.79 (m, 1H), 1.14 (s, 9H), 1.20 (s, 9H), 1.40 (m, 1H), 1.75 (m, 1H), 2.74 (d, J=12.8 Hz, 1H), 3.35 (d, J=10.4 Hz, 1H), 3.36 (d, J=13.2 Hz, 1H), 3.68 (s, 1H), 4.18 (d, J=11.2 Hz, 1H), 4.63 (s, 1H), 4.91 (s, 1H), 7.36–7.46 (m, 6H), 7.64–7.69 (m, 4H), 8.46 (s, 1H), 8.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.5, 19.4, 24.2, 27.3, 29.2, 36.5, 54.3, 64.7, 65.4, 72.0, 75.8, 84.3, 128.0, 128.1, 130.2, 130.3, 131.9, 132.9, 135.8, 136.0, 145.7, 151.5, 152.2, 152.4; $[\alpha]_D^{21.2}$ −54.5 (*c* 1.23, MeOH); IR (neat) 2105.63 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{33}H_{41}ClN_7O_3Si$ $[M+H]^+$: 646.2723; found: 646.2769.

*4.2.22. (−)-(1R,2R,3R,4R,5R)-2-tert-Butoxy-1-(tert-butyl-diphenyl-silanyloxymethyl)-4-(6-chloro-purin-9-yl)-3-fluoromethyl-bicyclo[3.1.0]hexan-3-ol (**29**).* Using the similar procedure used in the preparation of **18**, compound **27** (65.1 mg, 0.122 mmol) was converted to **29** (41.5 mg, 55%) as a colourless syrup: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 0.70 (m, 1H), 1.17 (s, 9H), 1.20 (s, 9H), 1.50–1.58 (m, 2H), 3.30 (d, J=11.2 Hz, 1H), 3.49 (d, J=0.8 Hz, 1H), 3.82 (dd, J=10.4, 46.8 Hz, 1H), 4.04 (dd, J=10.4, 48.0 Hz, 1H), 4.21 (d, J=10.8 Hz, 1H), 4.93 (s, 1H), 5.17 (s, 1H), 7.35–7.48 (m, 6H), 7.61–7.69 (m, 4H), 8.74 (s, 1H), 8.75 (s, 1H); ^{19}F NMR (CD_3OD) δ −222.09 (d, J=47.0 Hz); IR (neat) 3450.67, 1590.33, 1561.64, 1064.62, 703.16 cm^{-1}.

*4.2.23. (−)-(1R,2R,3R,4R,5R)-3-Azidomethyl-4-(6-chloro-purin-9-yl)-1-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**30**).* To a solution of **28** (53.9 mg, 0.083 mmol) in tetrahydrofuran (2 mL) was added tetra-*n*-butylammonium fluoride (0.1 mL, 0.100 mmol, 1.0 M solution in tetrahydrofuran) at 0 °C, and the reaction mixture was stirred at rt for 1 h. After evaporation, the residue was purified by silica gel column chromatography (hexane/ethyl acetate=2/1) to give diol (33 mg, 97%) as a colourless syrup: UV (MeOH) λ_{max} 266 nm; ^{1}H NMR ($CDCl_3$) δ 0.72 (m, 1H), 1.35 (s, 9H), 1.48 (m, 1H), 1.55 (m, 1H), 2.42 (d, J=12.8 Hz, 1H), 3.17 (d, J=11.6 Hz, 1H), 3.22 (d, J=13.2 Hz, 1H), 3.85 (s, 1H), 4.26 (d, J=11.6 Hz, 1H), 4.73 (s, 1H), 4.96 (s, 1H), 8.31 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$) 12.0, 25.4, 29.4, 37.5, 56.4, 64.9, 66.2, 72.0, 76.0, 83.4, 133.0, 148.3, 151.1, 151.5, 152.6; $[\alpha]_D^{19.5}$ −95.8 (*c* 1.03, MeOH); IR (neat) 2105.49 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{17}H_{23}ClN_7O_3$ $[M+H]^+$: 408.1545; found: 408.1543.

A solution of diol (30.0 mg, 0.074 mmol) in 70% aqueous trifluoroacetic acid (2 mL) was stirred at rt for 30 min, and the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol=20/1) to give **30** (17.5 mg, 68%) as a colourless syrup: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR (CD_3OD) δ 0.77 (m, 1H), 1.60 (m, 1H), 1.74 (m, 1H), 2.62 (d, J=13.2 Hz, 1H), 3.16 (d, J=13.6 Hz, 1H), 3.36 (d, J=14.0 Hz, 1H), 3.37 (d, J=11.6 Hz, 1H), 4.28 (d, J=11.6 Hz, 1H), 4.64 (s, 1H), 5.17 (s, 1H), 8.76 (s, 1H), 8.99 (s, 1H); ^{13}C NMR (CD_3OD) δ 12.5, 25.0, 38.0, 56.9, 64.1, 64.6, 73.9, 83.0, 132.5, 148.2, 151.6, 153.1, 153.4; $[\alpha]_D^{21}$ −90.1 (*c* 0.85, MeOH); IR (neat) 2106.47 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{13}H_{15}ClN_7O_3$ $[M+H]^+$: 352.0919; found: 352.0919.

*4.2.24. (−)-(1R,2R,3R,4R,5R)-4-(6-Chloro-purin-9-yl)-3-fluoromethyl-1-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**31**).* Using the similar procedure used in the preparation of **30**, compound **29** (82.3 mg, 0.132 mmol) was converted to diol (54.8 mg, 92%) as a colourless syrup: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR ($CDCl_3$) δ 0.75 (ddd, J=1.6, 6.0 and 8.8 Hz, 1H), 1.33 (s, 9H), 1.54 (dd, J=4.0, 5.6 Hz, 1H), 1.62 (m, 1H), 3.22 (d, J=11.6 Hz, 1H), 3.67 (s, 1H), 3.79 (dd, J=10.4, 47.6 Hz, 1H), 4.02 (dd, J=10.4, 47.6 Hz, 1H), 4.32 (dd, J=8.4, 11.6 Hz, 1H), 4.71 (d, J=8.4 Hz, 1H), 4.95 (s, 1H), 5.00 (s, 1H), 8.45 (s, 1H), 8.74 (s, 1H); ^{19}F NMR (CD_3OD) δ −227.50 (d, J=47.0 Hz); ^{13}C NMR ($CDCl_3$) 12.2, 25.1, 29.1, 37.0, 64.7, 65.2, 69.2 (J=8.4 Hz), 76.0, 80.5 (J=16.9 Hz), 82.0, 83.8, 147.1, 151.5, 151.8, 152.2; $[\alpha]_D^{25.2}$ +3.4 (*c* 1.30, MeOH); IR (neat) 3356.37, 1592.75, 1399.27, 1206.23, 945.95 cm^{-1}; HR-ESIMS (*m*/*z*) calcd for $C_{17}H_{23}ClFN_4O_3$ $[M+H]^+$: 385.1437; found: 385.1440.

Using the similar procedure used in the preparation of **30**, diol (41.8 mg, 0.109 mmol) was converted to **31** (27.4 mg, 77%) as a colourless syrup: UV (MeOH) λ_{max} 265 nm; ^{1}H NMR (CD_3OD) δ 0.80 (ddd, J=1.2, 5.2 and 8.8 Hz, 1H), 1.67 (dd, J=4.0, 8.8 Hz, 1H), 1.80 (dd, J=4.0, 5.2 Hz, 1H), 3.33 (d, J=11.6 Hz, 1H), 3.82 (dd, J=10.0, 48.0 Hz, 1H), 4.00 (dd, J=10.0, 48.0 Hz, 1H), 4.35 (d, J=11.6 Hz, 1H), 4.78 (s, 1H), 5.19 (s, 1H), 8.75 (s, 1H), 9.09 (s, 1H); ^{19}F NMR (CD_3OD) δ −227.01 (d, J=47.4 Hz); ^{13}C NMR (CD_3OD) δ 12.7, 24.6, 37.5, 63.6,

64.5, 71.0 (J=4.8 Hz), 80.5 (J=16.1 Hz), 83.0, 84.7, 147.9, 151.3, 153.0, 153.8; $[\alpha]_D^{25.6}$ −19.5 (c 1.03, MeOH); IR (neat) 3354.21, 1593.57, 1565.30, 1401.37, 1341.09, 1202.06, 1020.10 cm^{-1}; HR-ESIMS (m/z) calcd for $C_{13}H_{15}ClFN_4O_3$ $[M+H]^+$: 329.0811; found: 329.0807.

*4.2.25. (−)-(1R,2R,3R,4R,5R)-4-(6-Amino-purin-9-yl)-3-azidomethyl-1-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**4e**).* A mixture of **30** (17.5 mg, 0.050 mmol) and saturated methanolic ammonia (2 mL) was stirred at 80 °C overnight, and the reaction mixture was evaporated. The residue was purified by silica gel column chromatography (methylene chloride/methanol=10/1) to give **4e** (10.9 mg, 66%) as a white solid after recrystallisation from methanol and the methoxy compound (5.3 mg, 31%) as a colourless syrup: mp 125.7–135.3 °C; UV (MeOH) λ_{max} 259 nm; ^1H NMR (CD_3OD) δ 0.70–0.74 (m, 1H), 1.57–1.60 (m, 1H), 1.67 (t, 1H), 2.58 (d, J=13.2 Hz, 1H), 3.12 (d, J=12.8 Hz, 1H), 3.29 (d, J=11.2 Hz, 1H), 4.28 (d, J=11.6 Hz, 1H), 4.65 (s, 1H), 4.98 (s, 1H), 8.18 (s, 1H), 8.41 (s, 1H); ^{13}C NMR (CD_3OD) δ 12.5, 25.1, 38.0, 57.2, 64.7, 65.0, 74.0, 83.0, 120.4, 143.3, 150.5, 153.7, 157.7; $[\alpha]_D^{21.7}$ −107.16 (c 1.09, MeOH); IR (neat) 2107.36 cm^{-1}; HR-ESIMS (m/z) calcd for $C_{13}H_{17}N_8O_3$ $[M+H]^+$: 333.1418; found: 333.1414. Anal. Calcd for $C_{13}H_{16}N_8O_3$: C, 46.98; H, 4.85; N, 33.72. Found: C, 46.99; H, 4.91; N, 33.42.

*4.2.26. (−)-(1R,2R,3R,4R,5R)-4-(6-Amino-purin-9-yl)-3-fluoromethyl-1-hydroxymethyl-bicyclo[3.1.0]hexane-2,3-diol (**4f**).* Using the similar procedure used in the preparation of **4e**, compound **31** (27.4 mg, 0.0834 mmol) was converted to **4f** (8.2 mg, 32%) as a white solid: mp 207.8–210.2 °C (decomp.); UV (MeOH) λ_{max} 260 nm; ^1H NMR (CD_3OD) δ 0.75 (ddd, J=1.6, 5.2 and 8.8 Hz, 1H), 1.64 (dd, J=4.0, 8.8 Hz, 1H), 1.73 (dd, J=4.0, 5.2 Hz, 1H), 3.29 (d, J=11.2 Hz, 1H), 3.78 (dd, J=10.0, 47.6 Hz, 1H), 4.00 (dd, J=10.0, 47.6 Hz, 1H), 4.32 (d, J=11.2 Hz, 1H), 4.75 (s, 1H), 5.00 (s, 1H), 8.18 (s, 1H), 8.49 (s, 1H); ^{19}F NMR (CD_3OD) δ −229.02; ^{13}C NMR (CD_3OD) δ 12.6, 24.8, 37.7, 64.0, 64.8, 71.4 (J=4.7 Hz), 81.0 (J=15.9 Hz), 83.7, 85.5, 142.8, 150.7, 153.6, 157.5; $[\alpha]_D^{21.7}$ −43.2 (c 0.78, MeOH); IR (neat) 3334.84, 1650.54, 1602.49, 1303.35, 1252.85, 1019.70 cm^{-1}; HR-ESIMS (m/z) calcd for $C_{13}H_{17}FN_5O_3$ $[M+H]^+$: 310.1310; found: 310.1308. Anal. Calcd for $C_{13}H_{16}FN_5O_3$: C, 50.48; H, 5.21; N, 22.64. Found: C, 50.49; H, 5.56; N, 22.34.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.11.052.

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