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DIVERSITY-ORIENTED SYNTHESIS OF 2-SUBSTITUTED PURINE NUCLEOSIDES FROM AVAILABLE NUCLEOSIDES VIA THE LATE-STAGE NITRATION/DERIVATIZATION

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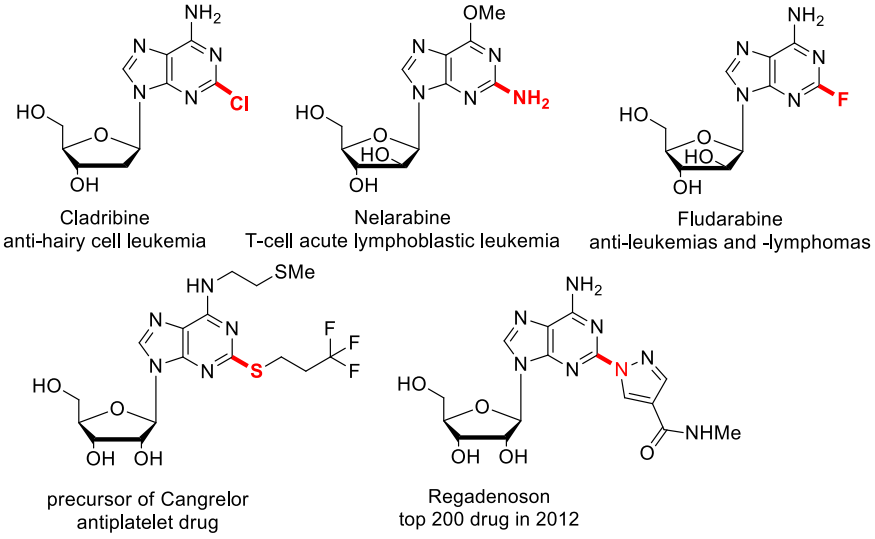
Abstract – A practical synthesis of 2-substituted purine nucleosides was developed in good to excellent yields from readily available nucleosides, such as adenosine, vidarabine and 2′-deoxyadenosine, via the late-stage nitration/derivatization. The C(2)-H bonds of purines were nitrated by 2,2,2-trifluoroacetic anhydride/Bu_4NNO_3, followed by nucleophilic substitution or hydrogenolysis reduction converting C(2)-NO_2 to C(2)-Cl, C(2)-F, C(2)-N, C(2)-O and C(2)-S bonds. This system could tolerate arabinofuranosyl, ribosyl, deoxyribosyl, -OH or -NH_2 groups. The clinical drugs, Regadenoson, Cladribine and Fludarabine, and the important naturally occurring nucleosides, spongosine and crotonoside, could be obtained successfully even on 20 g scales, which made this route more attractive for industrial applications.

INTRODUCTION

Nucleosides have displayed significant antivirus and anticancer activities.[1] In the context of the outbreak of COVID-19, nucleoside drugs have once again attracted the scientists' attention. For example, Remdesivir,[2] Molnupiravir[2] and Azvudine[3] have been used clinically. The increasing demand for nucleoside drugs and intermediates has pushed up the price of nucleoside raw materials. Thus, using cheap nucleosides as raw materials to produce high value-added nucleoside drugs or intermediates *via* innovative synthetic routes, has become an important way to meet clinical needs.[4]

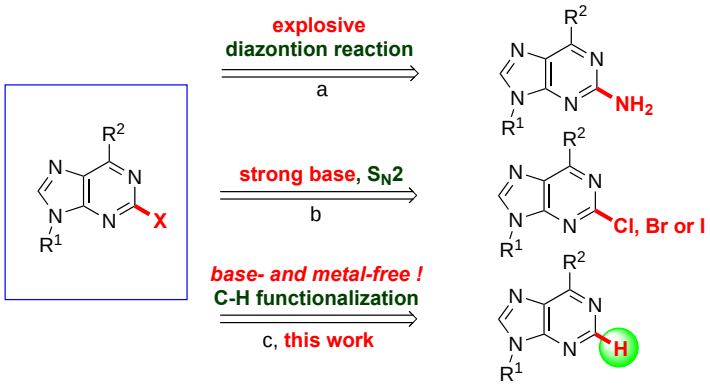
2-Substituted purine nucleosides have received considerable attention due to their broad spectrum of biological activities.[5] Thus, numerous economically important pharmaceuticals, such as Cladribine,[6] Regadenoson,[7] Fludarabine,[8] Cangrelor [9] or Nelarabine,[10] have 2-substituted purine units as indispensable

substructures (Scheme 1). However, the direct functionalization of C(2)-H remains more challenging than C(6) or C(8)[11] owing to the low reactivity of C(2)-H.



Scheme 1. Selected industrially important pharmaceuticals of 2-substituted purine nucleosides

Based on the pioneering studies, most of the available synthetic methods of 2-substituted purine nucleosides are relied on the diazotization of 2-NH_2 purines,[12] or nucleophlic substitution of 2-halo purines (Scheme 2).[13] The high price of 2-NH_2 or 2-halo purines and the harsh or explosive reaction conditions limit their applications in drug discoveries.

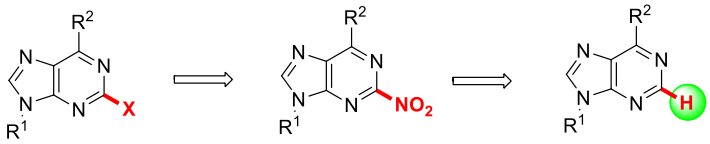


Scheme 2. The different strategies to 2-subtituted purine nucleosides

Compared to 2-NH_2 or 2-halo purines, the C(2)-H purine nucleosides such as adenosine (**1**), vidarabine (**2**) and 2′-deoxyadenosine (**3**) which cover the important nucleoside types such as ribosides, arabinosides and 2′-deoxyribosides respectively, have became more readily available recent years, because they can be produced in bulk by fermentation. The synthetic routes starting from these readily available starting materials will create opportunities for the synthesis of 2-substituted purine nucleosides. Although related

studies have been reported,[14] including our recent work,[15] they have not been used to systematically synthesize 2-substituted nucleosides and develop a practical synthetic route.

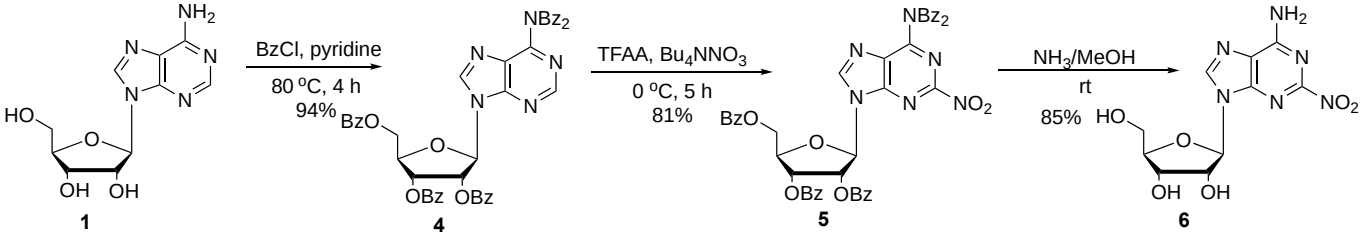
In the context of ongoing projects on the synthesis of nucleosides,[16-18] herein, we realized the practical synthesis of 2-substituted purine nucleosides from adenosine, vidarabine and 2′-deoxyadenosine (Scheme 2c). The corresponding retrosynthetic analysis is shown in Scheme 3.



Scheme 3. The retrosynthetic analysis

RESULTS AND DISCUSSION

Initially, the hydroxyl and amino groups of **1** were protected with benzoyl groups which were conducted with benzoyl chloride in pyridine at 80 ºC for 4 h to give **4** in 94% yield. The work-up process was improved to be more suitable for large-scale synthesis. The reaction scale could be enlarged to 200 grams and the chromatography was not required for purification.



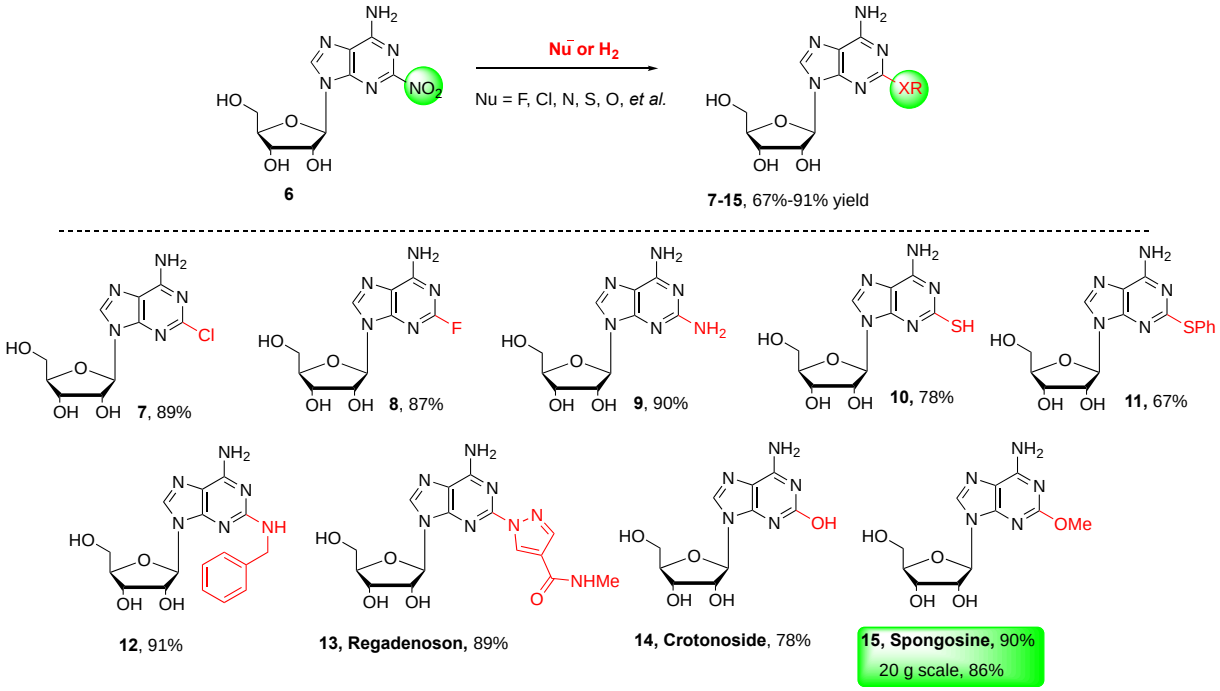
Scheme 4. The synthetic route of 2-nitroadenosine (**6**)

The nitration of **4** was realized by reacting with 2,2,2-trifluoroacetic anhydride (TFAA) and Bu_4NNO_3 in CH_2Cl_2. According to the pioneering work,[14] $F_3CCO_2NO_2$ as an nitration regent was produced *in situ*, and NO_2^+ reacted at C(2) of purine selectively to give 2-nitroadenosine (**6**) followed by the ammonolysis in NH_3/MeOH.

Next, we used **6** to synthesize a variety of 2-substituted adenosines *via* the derivation of C(2)-NO_2. 2-Chloro (**7**)[19] and 2-fluoroadenosine (**8**)[20] show interesting activities in several biological systems. Thus, the development of simple and efficient ways to construct these compounds is highly desirable. Herein, **6** could be converted into **7** and **8** in good yields using NH_4Cl and NH_4F in DMF respectively (Scheme 5). 2-Aminoadenosine (**9**) was obtained by the reduction of **6** in the presence of catalytic Ni in H_2 atmosphere. Thioadenosine derivatives were examined for the inhibitory effect of platelet aggregation in literatures.[21] 2-Thioadenosine (**10**) has been previously obtained from guanosine in less than 20% yield by 5-step synthesis.[22] In this article, **10** and 2-phenylthioadenosine (**11**) were provided in 56% and 67% yield in a

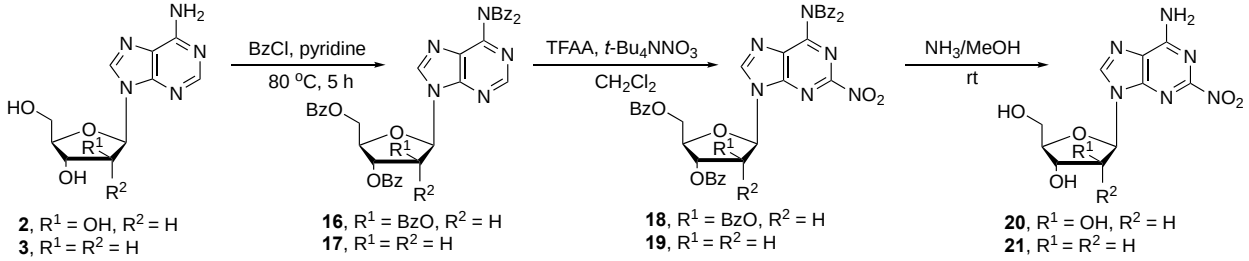
single step from **6** respectively. The compound **6** also could be transformed into 2-benzylaminoadenosine (**12**) by reacting with benzylamine in DMF. As a comparison, the nucleophilic substitution of benzylamine with 2-chloropurines needed 1 equivalent of sodium tetrafluoroborate as additive at 180 °C.[13] Methanolic ammonia could only remove the protecting groups, rather than substituting C(2)-NO_2 with ammonia. One possible reason was the poor nucleophilicity of ammonia (pKa of ammonia was 4.75, and pKa of benzylamine was 9.33). Likewise, Regadenoson (**13**), the top 200 drug in 2012, is an A2A adenosine receptor agonist and a coronary vasodilator which could also be synthesized from **6** in a single step. Compared to Cl, F, N or O atoms, the sulfur substituents gave lower yields (**10** and **11**).

This method is also very effective and robust in the synthesis of naturally occurring nucleosides. Crotonoside (**14**) was first isolated from Chinese medicinal herb Croton and exhibited selective inhibition of FLT3, HDAC3/6 and acute myeloid leukemia (AML) cells.[23] Herein, crotonoside was synthesized using Bu_4NOH in THF from **6**, providing more raw materials for further study of its activity. 2-Methoxyadenosine (**15**), also called spongosine, which was first isolated from sponge *Tectitethya crypta* and demonstrated a diverse bioactivity profile including anti-inflammatory activity and analgesic and vasodilation properties.[24] In this case, **15** was synthesized using MeONa in DMF from **6**.

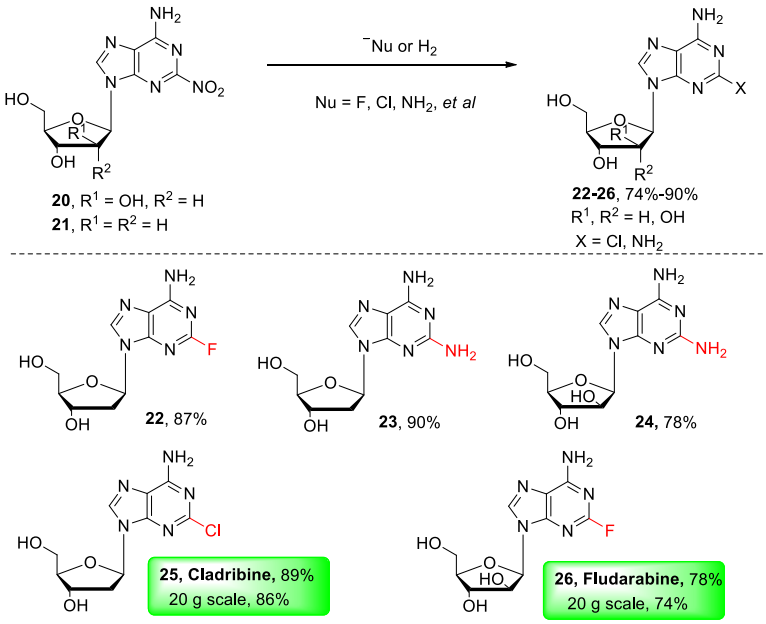


Scheme 5. The synthesis of 2-substituted adenosines

Like adenosine (**1**), Vidarabine (**2**) and 2′-deoxyladenosine (**3**) are also the most readily available starting materials and could be used as substrates to provide 2-substituted arabinosides and deoxyribosides (Scheme 6).



Scheme 6. The synthesis of nitrated 2-nitrovidarabine (**20**) and 2-nitro-2-deoxyladenosine (**21**)



Scheme 7. The synthetic route of 2-substituted arabinofuranosyl purines and deoxyribosyl purines

Following a similar approach, 2-nitrovidarabine (**20**) 2-nitro-2′-deoxyadenosine **(21)** were obtained from **2** and **3** respectively. Subsequently, a variety of arabinofuranosyl purines and deoxyribosyl purines were obtained in good yields (78%-90%) after transformation of nitro groups, including the clinical drugs, Cladribine **(25)** and Fludarabine **(26)**, for treating leukemia.

Reactions on large scales demonstrated the robustness and preparative scale utility of this process. Cladribine, Fludarabine and Spongosine could be obtained successfully on 20 g scales with comparable yields. More importantly, these nucleosides could be purified by recrystallization avoiding chromatography or lengthy work-up process, which made this route more attractive for industrial applications.

CONCLUSIONS

In summary, we described the practical synthesis of 2-substituted purine nucleosides from adenosine, vidarabine and 2′-deoxyadenosine. Purines were nitrated with TFAA/Bu_4NNO_3, followed by nucleophlic substitution or hydrogenolysis reduction to give C(2)-Cl, C(2)-F, C(2)-N, C(2)-O and C(2)-S substituted

purine nucleosides in good to excellent yields. These 2-substitued purine nucleosides were previously synthesized from lengthy steps and harsh conditions in lower yields. This system could tolerate arabinofuranosyl, ribosyl, deoxyribosyl, -OH or -NH_2 groups. More importantly, 3 clinical drugs and 2 naturally occurring nucleosides could be obtained successfully even on 20 g scales and chromatography was not required for purified step, which made it more attractive for industrial applications.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were determined on a Bruker AC 400 spectrometer (Bruker, Billerica, MA, USA) as DMSO-d_6 or $CDCl_3$ solution. Chemical shifts were expressed in parts permillion (δ) downfield from the internal standard tetramethylsilane and were reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and dd (doublet of doublets) and coupling constants *J* were given in hertz (Hz). The high-resolution mass spectra (HRMS) was taken using Q-TOF system, with Electrospray Ionization (ESI) as the ionization method. All reactions were monitored by thin layer chromatography (TLC). All reagents and solvents were purchased from commercial sources and purified commonly before used.

(2*R*,3*R*,4*R*,5*R*)-2-(6-(N-Benzoylbenzamido)-9*H*-purin-9-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (4). Benzoyl chloride (1.15 mL, 10 mmol) was slowly added to a magnetically stirred suspension of adenosine (**1**, 0.534 g, 2 mmol) in pyridine (3 mL). The mixture was heated to 80 ^{o}C and kept at this temperature for 4 h. After cooling to 0 ^{o}C, the reaction mixture was neutralized by 1 mol/L aqueous HCl and was extracted by CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried on anhydrous Na_2SO_4 and concentrated *in vacuo*. The resulting residue was recrystallized from EtOH to give **4** as a white solid (1.48 g, 94% yield).

The procedure of 200 g scale for 4: Adenosine (200 g, 749 mmol) was added to pyridine (1 L), cooled to 0 ^{o}C and stirred for 1 h to give a suspension followed by the addition of benzoyl chloride (432 mL, 3.75 mol). Upon the completion, the mixture was stirred and heated to 80 ^{o}C for 8 h. The reaction mixture was cooled to 0 ^{o}C and neutralized by 1 mol/L HCl. The neutralized mixture was extracted with CH_2Cl_2 (500 mL × 3). The combined organic layers were washed with brine (1 L), decolored by activated carbon (20 g), dried on anhydrous Na_2SO_4 and concentrated *in vacuo*. EtOH (500 mL) was added to the residue and then removed *in vacuo* to remove the residual pyridine. The resulting syrup was dissolved in EtOH (800 mL) under heating conditions, and then cooled. The forming solid **4** was filtrated. The mother liquor was concentrated and recrystallized from EtOH to give the other batch of **4** (531 g, 90% yield).

Other compounds **16** and **17** were synthesized similarly.

***(2R,3R,4R,5R)*-2-(6-(N-Benzoylbenzamido)-9*H*-purin-9-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (4):** a white solid, 94% yield; mp 180-182 ^{o}C (lit.[25] 181 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.22 (s, 1H), 8.10-8.03 (m, 10H), 7.60-7.33 (m, 10H), 6.48 (d, *J* = 5.2 Hz, 1H),

6.39 (t, *J* = 5.2 Hz, 1H), 6.26 (t, *J* = 5.2 Hz, 1H), 4.92-4.83 (m, 2H), 4.73-4.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 166.2, 165.3, 165.1, 152.7, 152.5, 152.1, 143.6, 134.0, 133.9, 133.8, 133.5, 133.1, 129.9, 129.8, 129.5, 129.3, 129.0, 128.8, 128.7, 128.6, 127.9, 87.2, 80.9, 73.8, 71.4, 63.6. HRMS calcd for $C_{45}H_{34}N_5O_9$ $[M+H]^+$ 788.2351, found 788.2350.

(2*R*,3*S*,4*R*,5*R*)-2-(6-(N-Benzoylbenzamido)-9*H*-purin-9-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (16): a white solid, 91% yield; mp 232-234 °C (lit.[26] 232-234 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 8.68 (s, 1H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.74-7.35 (m, 21H), 6.97 (t, *J* = 6.4 Hz, 1H), 6.36 (t, *J* = 5.6 Hz, 1H), 6.23 (t, *J* = 6.0, 1H), 4.84-4.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 166.0, 165.5, 164.7, 153.0, 152.5, 151.6, 146.8, 134.5, 134.4, 134.0, 133.9, 133.8, 129.7, 129.6, 129.4, 129.3, 129.1, 95.4, 83.0, 77.8, 76.2, 64.2. HRMS calcd for $C_{45}H_{34}N_5O_9$ $[M+H]^+$ 788.2351, found 788.2350.

(2*R*,3*S*,5*R*)-5-(6-(N-Benzoylbenzamido)-9*H*-puryin-9-yl)-2-((benzoyloxy)methyl)tetrahydrofuran-3-yl benzoate (17): a white solid, 94% yield; mp 172-174 °C (lit.[27] 173-174 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.24 (s, 1H), 8.10 (d, *J* = 7.2 Hz, 2H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 4H), 7.63-7.34 (m, 12H), 6.58 (dd, *J* = 6.0 Hz, 8.4 Hz, 1H), 5.86 (d, *J* = 6.4 Hz, 1H), 4.80-4.66 (m, 3H), 4.25-4.20 (m, 1H), 2.87-2.82 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.6, 166.0, 165.8, 152.9, 152.2, 151.5, 146.6, 134.2, 133.9, 133.8, 129.9, 129.7, 129.6, 129.5, 129.3, 129.2, 127.9, 84.9, 82.2, 75.2, 64.3, 35.8. HRMS calcd for $C_{38}H_{30}N_5O_7$ $[M+H]^+$ 668.2140, found 668.2140.

(2*R*,3*R*,4*R*,5*R*)-2-(6-(N-Benzoylbenzamido)-2-nitro-9*H*-purin-9-yl)-5-((benzoyloxy)methyl)tetrahydrofuran-3,4-diyl dibenzoate (5). The nitrating mixture was prepared by adding 2,2,2-trifluoroacetic anhydride (0.21 mL, 1.5 mmol) to a solution of tetrabutylammonium nitrate (0.457 g, 1.5 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C. After 20 min the nitrating mixture was added to **4** (0.787 g, 1 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C. After 5 h at 0 °C, the reaction mixture was poured into a cold mixture of H_2O (10 mL), aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (5 mL). The aqueous phase was extracted by CH_2Cl_2 (5 mL × 2). The combined organic extracts were washed with brine (10 mL × 2), dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The product **5** was recrystallized from EtOH (0.67 g, 80% yield); a white solid, mp 130-132 °C (lit.[25] 130 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.07-8.02 (m, 4H), 7.94. (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 7.6 Hz, 4H), 7.62-7.50 (m, 5H), 7.45-7.35 (m, 10H), 6.59 (d, *J* = 5.2 Hz, 1H), 6.17 (t, *J* = 4.8 Hz, 1H), 6.09 (d, *J* = 5.2 Hz, 1H), 4.95-4.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 166.1, 165.4, 165.3, 153.7, 152.9, 134.1, 133.9, 133.6, 133.4, 130.0, 129.9, 129.7, 129.6, 129.1, 129.0, 128.7, 128.5, 128.0, 87.3, 81.7, 74.8, 71.6, 63.8. HRMS calcd for $C_{45}H_{32}N_6NaO_{11}$ $[M+Na]^+$ 855.2021, found 855.2025.

Other compounds **18** and **19** were synthesized similarly.

(2*R*,3*S*,4*R*,5*R*)-2-(6-(N-Benzoylbenzamido)-2-nitro-9*H*-purin-9-yl)-5-((benzoyloxy)methyl)tetra-

hydrofuran-3,4-diyl dibenzoate (18): a white foam, 82% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.10 (d, *J* = 7.2 Hz, 2H), 8.00 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 4H), 7.58-7.34 (m, 15H), 6.48 (t, *J* = 5.2 Hz, 1H), 6.39 (t, *J* = 5.2 Hz, 1H), 6.26 (t, *J* = 5.2 Hz, 1H), 4.92-4.88 (m, 1H), 4.85-4.82 (m, 1H), 4.73-4.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.4, 164.7, 155.5, 153.2, 149.5, 139.7, 134.0, 133.9, 133.3, 130.0, 129.8, 129.7, 129.5, 128.7, 128.6, 128.5, 127.9, 119.3, 80.8, 80.4, 75.8, 63.5. HRMS calcd for $C_{45}H_{33}N_6O_{11}$ $[M+H]^+$ 833.2202, found 833.2206.

(2*R*,3*S*,5*R*)-5-(6-(N-Benzoylbenzamido)-2-nitro-9*H*-purin-9-yl)-2-((benzoyloxy)methyl)tetrahydrofuran-3-yl benzoate (19): a yellow semisolid, 78% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.04 (d, *J* = 7.2 Hz, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 4H), 7.68-7.40 (m, 12H), 6.62 (t, *J* = 3.2 Hz, 1H), 5.85 (d, *J* = 6.4 Hz, 1H), 4.65-4.54 (m, 3H), 3.45-3.36 (m, 1H), 2.84-2.79 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2, 165.7, 165.5, 152.6, 151.9, 151.2, 146.3, 133.9, 133.6, 133.5, 129.6, 129.4, 129.3, 129.2, 128.9, 127.6, 84.5, 81.9, 74.8, 64.0, 35.5. HRMS calcd for $C_{38}H_{29}N_6O_9$ $[M+H]^+$ 713.1991, found 713.1993.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-2-nitro-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (6). Compound **5** (0.83 g, 1 mmol) and saturated NH_3/MeOH solution (20 mL) were added to the reaction vessel at 0 °C, sealed and stirred at room temperature for 24 h. The resulting solution was concentrated *in vacuo* and recrystallized from H_2O to give **6** (0.26 g, 85% yield); a white solid, mp 218-220 °C (lit.[14] 218-220 °C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.36 (s, 1H), 7.82 (brs, 2H), 5.81 (d, *J* = 6.0 Hz, 1H), 5.46 (d, *J* = 6.0 Hz, 1H), 5.19 (d, *J* = 4.8 Hz, 1H), 5.07 (t, *J* = 5.6 Hz, 1H), 4.52 (q, *J* = 5.6 Hz, 1H), 4.12 (d, *J* = 3.2 Hz, 1H), 3.94 (d, *J* = 2.8 Hz, 1H), 3.67-3.51 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.3, 152.9, 149.8, 140.8, 118.7, 84.5, 84.0, 76.1, 75.4, 61.3. HRMS calcd for $C_{10}H_{13}N_6O_6$ $[M+H]^+$ 313.0891, found 313.0891.

Other compounds **20** and **21** were synthesized similarly.

(2*R*,3*S*,5*R*)-5-(6-Amino-2-nitro-9*H*-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (20): a white solid; mp 166-168 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.53 (brs, 2H), 6.01 (d, *J* = 6.0 Hz, 1H), 5.69 (d, *J* = 5.6 Hz, 1H), 5.59 (d, *J* = 4.0 Hz, 1H), 5.16 (s, 1H), 4.05-4.03 (m, 2H), 3.76-3.72 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.9, 153.6, 151.0, 136.9, 115.6, 84.1, 83.3, 75.4, 75.2, 60.9. HRMS calcd for $C_{10}H_{13}N_6O_6$ $[M+H]^+$ 313.0891, found 313.0891.

(2*R*,3*S*,5*R*)-5-(6-Amino-2-nitro-9*H*-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (21): a white solid; mp 262-264 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.64 (brs, 2H), 6.06 (d, *J* = 6.0 Hz, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 5.50 (d, *J* = 4.0 Hz, 1H), 5.11 (t, *J* = 5.2 Hz, 1H), 3.75-3.71 (m, 1H), 3.67-3.56 (m, 2H), 3.16-3.09 (m, 1H) , 2.84-2.78 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 156.4, 152.0, 137.6, 112.9, 84.5, 83.7, 76.0, 61.6, 38.2; HRMS calcd for $C_{10}H_{13}N_6O_5$ $[M+H]^+$ 297.0942, found 297.0946.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-2-chloro-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (7). NH_4Cl (0.08 g, 1.5 mmol) and compound **6** (0.31 g, 1.0 mmol) were added to DMF (10 mL) and stirred for 4 h at room temperature. The resulting solution was concentrated *in vacuo* and recrystallized from EtOH to give **7** (0.27 g, 89% yield); a white solid; mp 144-146 ºC (lit.[27]145-147 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.83 (brs, 2H), 5.81 (d, *J* = 6.0 Hz, 1H), 5.47 (d, *J* = 6.0 Hz, 1H), 5.19 (d, *J* = 4.8 Hz, 1H), 5.05 (t, *J* = 5.6 Hz, 1H), 4.52 (q, *J* = 5.6 Hz, 1H), 4.12 (q, *J* = 4.0 Hz, 1H), 3.93 (d, *J* = 3.6 Hz, 1H), 3.67-3.62 (m, 1H), 3.56-3.51 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 152.9, 149.5, 140.4, 119.8, 88.4, 86.4, 73.9, 71.2, 62.2. HRMS calcd for $C_{10}H_{13}ClN_5O_4$ $[M+H]^+$ 302.0651, found 302.0653.

Other compounds **8, 10-15, 22, 25** and **26** were synthesized similarly.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-2-fluoro-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (8): 1.5 mmol NH_4F instead of NH_4Cl in the reaction conditions of **7**, 4 h, 87% yield; a white solid; mp 230-232 ºC. (decomp. lit.[29] 232 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 6.94 (brs, 2H), 6.26 (d, *J* = 4.8 Hz, 1H), 5.65 (d, *J* = 4.8 Hz, 1H), 5.57 (d, *J* = 4.4 Hz, 1H), 5.07 (t, *J* = 5.2 Hz, 1H), 4.35 (t, *J* = 5.2 Hz, 1H), 3.82 (q, *J* = 4.4 Hz, 1H), 3.45-3.39 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 158.0, 157.8, 151.2, 151.0, 141.1, 117.1, 117.0, 84.5, 84.2, 75.1, 75.0, 61.2. HRMS calcd for $C_{10}H_{13}FN_5O_4$ $[M+H]^+$ 286.0946, found 286.0948.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-2-mercapto-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (10): 1.5 mmol Na_2S instead of NH_4Cl in the reaction conditions of **7**, 4 h, 78% yield; a yellow solid; mp 196-198 ºC (lit.[22] 196-199 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.34 (brs, 1H), 8.33 (s, 1H), 7.28 (brs, 2H), 5.93 (d, *J* = 6.0 Hz, 1H), 5.58 (s, 1H), 5.44 (s, 1H), 5.08 (t, *J* = 4.8 Hz, 1H), 4.75 (d, *J* = 4.8 Hz, 1H), 4.22 (s, 1H), 4.09 (t, *J* = 4.0 Hz, 1H), 3.96-3.81 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 152.9, 149.5, 140.4, 119.8, 88.4, 86.4, 73.9, 73.1, 62.2. HRMS calcd for $C_{10}H_{13}N_5NaO_4S$ $[M+Na]^+$ 322.0580, found 322.0580.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-2-(phenylthio)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (11): 1.5 mmol PhSNa instead of NH_4Cl in the reaction conditions of **7**, 4 h, 67% yield; a yellow solid; mp 210-212 ºC (lit.[30] 210 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (brs, 1H), 7.38-7.30 (m, 5H), 7.00 (brs, 2H), 6.01 (d, *J* = 4.4 Hz, 1H), 5.69 (d, *J* = 4.8 Hz, 1H), 5.92 (d, *J* = 2.0 Hz, 1H), 5.16 (s, 1H), 4.05 (t, *J* = 4.0 Hz, 1H), 3.74 (t, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.4, 152.0, 149.4, 140.4, 128.1, 127.0, 126.1, 119.5, 87.7, 85.8, 74.4, 70.9, 62.1. HRMS calcd for $C_{16}H_{18}N_5O_4S$ $[M+H]^+$ 376.1074, found 376.1078.

(2*R*,3*R*,4*S*,5*R*)-2-(6-Amino-2-(benzylamino)-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (12): 1.5 mmol Benzylamine instead of NH_4Cl in the reaction conditions of **7**, 8 h, 91% yield; a white solid; mp 118-120 ºC (lit.[31] 118-120 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.39-7.31

(m, 5H), 6.93 (brs, 2H), 6.54 (brs, 1H), 6.04 (d, *J* = 5.6 Hz, 1H), 5.92 (brs, 1H), 5.21 (brs, 1H), 4.78 (brs, 2H), 4.62 (t, *J* = 5.2 Hz, 1H), 4.19 (t, *J* = 4.0 Hz, 1H), 3.97 (t, *J* = 3.6 Hz, 1H), 3.69-3.39 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 152.3, 149.2, 140.0, 129.3, 128.6, 127.9, 118.9, 87.8, 85.0, 69.1, 61.9, 60.0, 46.2. HRMS calcd for $C_{17}H_{21}N_6O_4$ $[M+H]^+$ 373.1619, found 373.1617.

1-(6-Amino-9-((2*R*,3*R*,4*S*,5*R*)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-9*H*-purin-2-yl)-N-methyl-1*H*-pyrazole-4-carboxamide (13): 1.5 mmol Sodium 4-(methylcarbamoyl)pyrazol-1-ide instead of NH_4Cl in the reaction conditions of **7**, 8 h, 50 ºC, 89% yield; a white solid; mp 259-260 ºC (lit.[31] 260.7 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 8.10 (s, 1H),7.87 (s, 1H), 7.65 (brs, 1H), 6.94 (brs, 2H), 5.82 (d, *J* = 4.0 Hz, 1H), 5.62 (d, *J* = 5.6 Hz, 1H), 5.24 (d, *J* = 5.6 Hz, 1H), 4.96 (t, *J* = 5.2 Hz, 1H), 4.37 (q, *J* = 5.6 Hz, 1H), 4.15 (q, *J* = 3.2 Hz, 1H), 3.96 (q, *J* = 2.8 Hz, 1H), 3.64-3.37 (m, 2H), 2.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 157.3, 152.0, 149.7, 140.2, 136.4, 134.1, 119.7, 111.2, 91.7, 85.5, 74.5, 69.9, 61.3, 26.1. HRMS calcd for $C_{15}H_{19}N_8O_5$ $[M+H]^+$ 391.1473, found 391.1475.

Crotonside (14): 1.5 mmol Bu_4NOH instead of NH_4Cl in the reaction conditions of **7**, 8 h, 50 ºC, 78% yield; a white solid; mp 238-24 ºC (lit.[32] 238-24 ºC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.88 (s, 1H), 8.37 (s, 1H), 7.83 (brs, 2H), 5.81 (d, *J* = 6.0 Hz, 1H), 5.47 (d, *J* = 6.0 Hz, 1H), 5.19 (d, *J* = 4.8 Hz, 1H), 5.05 (t, *J* = 4.8 Hz, 1H), 4.52-4.48 (m, 1H), 4.12-4.09 (m, 1H), 3.93 (d, *J* = 3.6 Hz, 1H), 3.67-3.52 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 160.2, 156.0, 151.6, 137.1, 112.4, 84.1, 83.3, 75.6, 61.1. HRMS calcd for $C_{10}H_{14}N_5O_5$ $[M+H]^+$ 284.0989, found 284.0989.

Spongosine (15): 1.5 mmol MeONa instead of NH_4Cl in the reaction conditions of **7**, 3 h, 90% yield; a white solid; mp 190-192 ºC (lit.[33] 190-192 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.83 (brs, 2H), 5.81 (d, *J* = 6.0 Hz, 1H), 5.47 (d, *J* = 6.0 Hz, 1H), 5.19 (d, *J* = 4.8 Hz, 1H), 5.07 (d, *J* = 5.6 Hz, 1H), 4.52 (q, *J* = 5.6 Hz, 1H), 4.12 (d, *J* = 4.0 Hz, 1H), 3.93 (d, *J* = 3.6 Hz, 1H), 3.80 (s, 3H), 3.67-3.62 (m, 2H), 3.56-3.52 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 152.9, 149.3, 139.5, 119.6, 91.3, 81.2, 75.1, 63.1, 45.6. HRMS calcd for $C_{11}H_{16}N_5O_5$ $[M+H]^+$ 298.1146, found 298.1146.

(2*R*,3*S*,5*R*)-5-(6-Amino-2-fluoro-9*H*-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (22): 1.50 mmol NH_4F instead of NH_4Cl in the reaction conditions of **7**, 6 h, 87% yield; a white solid; mp 210 ºC (decomp. lit.[34] 210 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.73 (brs, 2H), 6.10 (d, *J* = 4.8 Hz, 1H), 5.64 (d, *J* = 5.2 Hz, 1H), 5.56 (d, *J* = 4.8 Hz, 1H), 5.10 (t, *J* = 5.2 Hz, 1H), 4.16-4.09 (m, 1H), 3.78-3.75 (m, 1H), 3.67-3.60 (m, 1H), 2.85-2.79 (m, 1H), 2.35-2.28 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 158.0, 157.8, 151.2, 151.0, 141.1, 117.1, 117.0, 87.1, 84.2, 70.1, 70.0, 61.2, 38.2. HRMS calcd for $C_{10}H_{13}FN_5O_3$ $[M+H]^+$ 270.0997, found 270.0993.

Cladribine (25): 4 h, 50 ºC, 89% yield; a white solid. mp 302-306 ºC (decomp. lit.[35] 306-310 ºC); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.34 (brs, 2H), 6.35 (d, *J* = 4.8 Hz, 1H), 5.36 (t, *J* = 5.2 Hz, 1H), 5.31 (t, *J* = 4.8 Hz, 1H), 4.41 (d, *J* = 5.2 Hz, 1H), 3.88 (d, *J* = 5.2 Hz, 1H), 3.64-3.59 (m, 1H),

2.75-2.69 (m, 1H), 2.45-2.38 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.0, 152.4, 139.6, 119.2, 88.0, 83.9, 71.0, 61.9, 36.8. HRMS calcd for $C_{10}H_{13}ClN_5O_3$ $[M+H]^+$ 286.0701, found 286.0701.

Fludarabine (26): 1.5 mmol NH_4F instead of NH_4Cl in the reaction conditions of **7**, 6 h, 78% yield; a white solid; mp 264-266 °C (lit.[36] 265-267 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.80 (brs, 2H), 6.12 (d, *J* = 4.8 Hz, 1H), 5.66 (d, *J* = 5.2 Hz, 1H), 5.56 (d, *J* = 4.4 Hz, 1H), 5.09 (t, *J* = 5.6 Hz, 1H), 4.17-4.11 (m, 2H), 3.79 (q, *J* = 4.4 Hz, 1H), 3.71-3.61 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.0, 158.0, 157.8, 151.2, 151.0, 141.0, 117.1, 117.0, 84.4, 84.0, 76.0, 75.0, 61.1. HRMS calcd for $C_{10}H_{12}FN_5NaO_4$ $[M+Na]^+$ 308.0766, found 308.0768.

(2*R*,3*R*,4*S*,5*R*)-2-(2,6-Diamino-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (9). Compound **6** (0.31 g, 1.0 mmol) was added to MeOH (5 mL) followed by the addition of Raney Ni (0.1 g). The reaction was conducted in H_2 atmosphere for 5 h. The mixture was filtrated and the filtrate was concentrated to dryness. The residue was recrystallized from H_2O to give **9** (0.25 g, 90% yield); a white solid; mp 240-242 °C. (lit.[37] 240 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 1H), 7.30 (brs, 2H), 6.21 (brs, 2H), 5.90 (d, *J* = 5.6 Hz, 1H), 5.66 (brs, 1H), 5.50 (brs, 1H), 5.43 (brs, 1H), 4.64 (t, *J* = 5.2 Hz, 1H), 4.17 (t, *J* = 3.6 Hz, 1H), 4.10 (q, *J* = 5.2 Hz, 1H), 3.93 (ddd, *J* = 4.8 Hz, 11.6 Hz, 16.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6, 152.9, 149.5, 140.4, 119.8, 88.4, 86.4, 73.9, 71.2, 62.2. HRMS calcd for $C_{10}H_{15}N_6O_4$ $[M+H]^+$ 283.1149, found 283.1145.

23 and **24** were synthesized similarly.

(2*R*,3*S*,5*R*)-5-(2,6-Diamino-9*H*-purin-9-yl)-2-(hydroxymethyl)tetrahydrofuran-3-ol (23): 90% yield; a white solid; mp 146-148 °C (lit.[38] 147-149 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (s, 1H), 7.34 (brs, 2H), 6.35 (t, *J* = 6.0 Hz, 1H), 6.18 (brs, 2H), 5.36 (brs, 1H), 5.29 (brs, 1H), 4.41 (d, *J* = 2.0 Hz, 1H), 3.88 (d, *J* = 2.4 Hz, 1H), 3.64-3.59 (m, 1H), 3.75-3.69 (m, 1H), 2.28-2.22 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.9, 152.2, 139.4, 119.0, 87.8, 83.8, 70.8, 61.7, 38.6. HRMS calcd for $C_{10}H_{15}N_6O_3$ $[M+H]^+$ 267.1200, found 267.1208.

(2*R*,3*S*,4*S*,5*R*)-2-(2,6-Diamino-9*H*-purin-9-yl)-5-(hydroxymethyl)tetrahydrofuran-3,4-diol (24): 8 h, 78% yield; a white solid; mp 260-262 °C (lit.[26] 260-262 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (s, 1H), 6.64 (brs, 2H), 6.05 (d, *J* = 4.4 Hz, 1H), 5.75 (brs, 2H), 5.62 (d, *J* = 5.2 Hz, 1H), 5.50 (d, *J* = 4.4 Hz, 1H), 5.11 (t, *J* = 5.2 Hz, 1H), 4.07-4.01 (m, 2H), 3.74 (d, *J* = 4.4 Hz, 1H), 3.45-3.06 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 156.4, 152.0, 137.6, 112.9, 84.5, 83.7, 76.0, 61.6. HRMS calcd for $C_{10}H_{15}N_6O_4$ $[M + H]^+$ 283.1149, found 283.1151.

The procedure of 2 on 20 g scale: NH_4F (3.8 g, 96.8 mmol) and compound **23** (20 g, 64.5 mmol) were added to DMF (300 mL) and the mixture was stirred for 12 h at room temperature. The resulting solution was concentrated *in vacuo*. The residue was acetylated in acetic anhydride in 60 °C for 2 h and concentrated *in vacuo*. The crude acetylated product was dissolved in CH_2Cl_2 (200 mL) and washed by

H_2O (100 mL). The organic phase was concentrated *in vacuo* and recrystallized from EtOH. The solid acetylated product was deacetylated in NH_3/MeOH (200 mL) for 12 h at room temperature. The resulting solution was concentrated *in vacuo* and recrystallized from H_2O to give **28**.

The procedure of 17 on 20 g scale: Compound **11** (20.0 g, 64.5 mmol) was dissolved in MeOH (300 mL) under stirring followed by the addition of MeONa (5.42 g, 96.8 mmol). The mixture was stirred for 3 h at room temperature. The resulting solution was concentrated *in vacuo* and recrystallized from isopropanol/H_2O (5/1) to give **17**. The mother liquor was flushed through a short silicon colum, concentrated *in vacuo* and recrystallized from isopropanol/H_2O (5/1) to give the other batch of **17**.

The procedure of 25 on 20 g scale: NH_4Cl (5.47 g, 101.35 mmol) and compound **24** (20.0 g, 67.57 mmol) were added to DMF (300 mL) and the mixture was stirred for 8 h at 50 ^oC. The resulting solution was concentrated *in vacuo* and recrystallized from MeOH to give **25**.

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SUPPORTING INFORMATION

Supplementary (^1H and ^{13}C NMR spectra) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27672/104/8

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