A synthetic approach to chiral carbocyclic nucleosides of varied ring-sizes using carbon framework of D-glucose

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Dedicated to Professor (Mrs.) Asima Chatterjee on her 85th birth anniversary
(received 27 Nov 03; accepted 15 Feb 04; published on the web 28 Feb 04)

Abstract
Synthesis of enantiomerically pure carbocyclic nucleoside analogues **10-16** with five-, six- and seven- membered rings has been achieved starting from D-glucose derived tetracyclic isoxazolidinocarbocycle precursors **1-3**. Cyclization of 6-chloro pyrimidine derivatives **7-9** to purine derivatives was found to be accomplished by nucleophilic displacement of 6-chloro substituent (by dimethylamino and/or methoxy groups). Apparently, hydrogen bonding between N-3 of the purine ring and a hydoxy substituent at C-2/ plays a crucial role in this transformation.

Keywords: Synthesis, chiral, carbocyclic nucleosides, D-glucose

Introduction

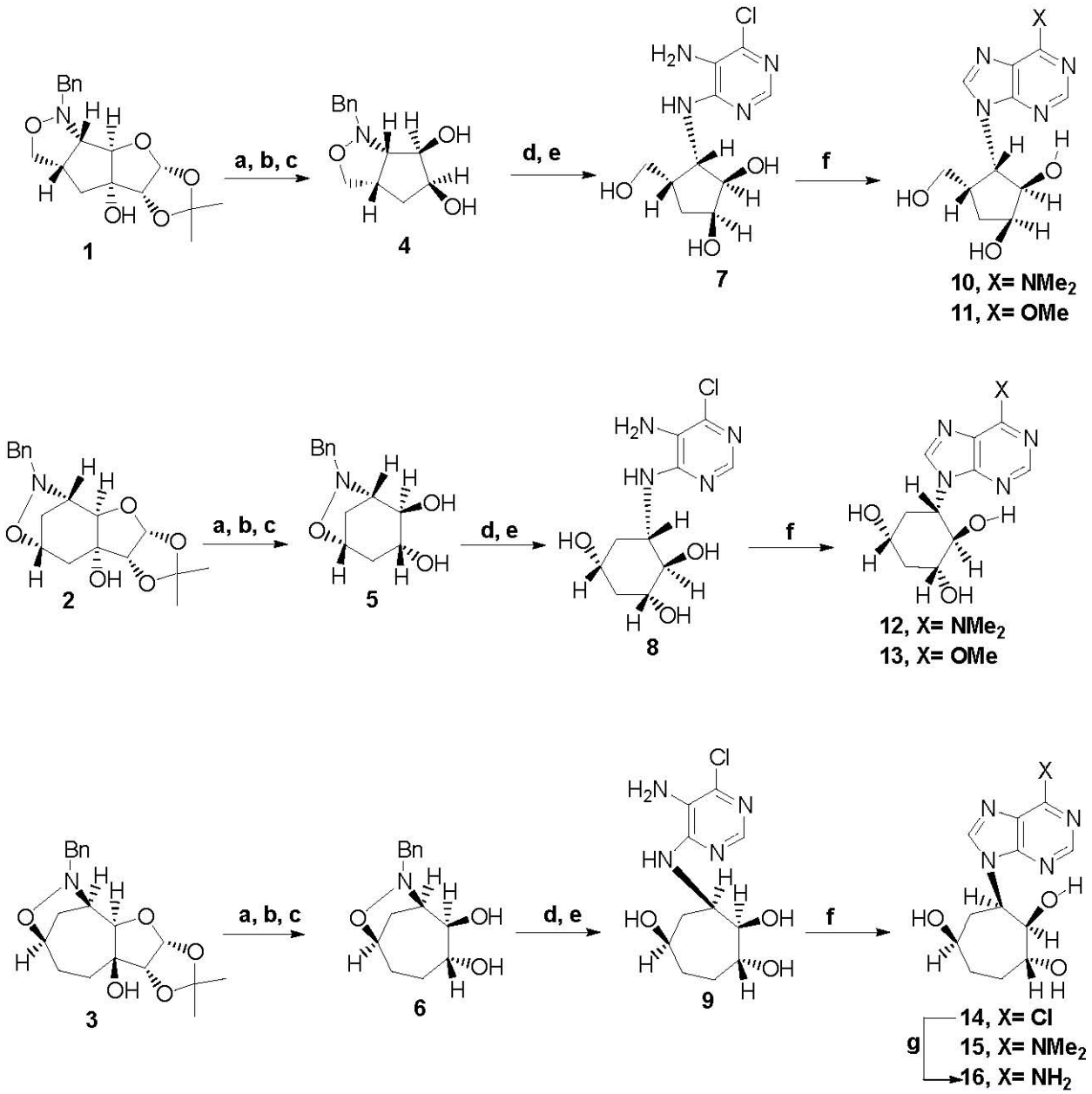
After the discovery of the two natural carbocyclic nucleosides (-)- aristeromycin[1] and (-)-neplanocin A[2] possessing antineoplastic activity, considerable attention was paid towards the synthesis of carbocyclic nucleosides with cyclopentane ring[3-4] over the last decade. But little effort has been paid towards the synthesis of such molecules with different ring sizes[5], particularly with six- and seven-membered rings. Besides, the realization that the biological activity normally resides in a particular enantiomer has given an impetus to the task of generating enantiomerically pure carbocyclic nucleosides. For an easy access to this class of chiral nucleosides, the synthesis of appropriate aminocarbocycles/hydroxycarbocycles in optically pure form is desirable. Though cyclopentadiene is often used for asymmetric synthesis of chiral amino- or hydroxy-cyclopentane derivatives[4], the other procedures to prepare these carbocycles involve (i) ring closing metathesis reaction between two olefins[6], (ii) manipulative degradation of norbornadiene skeleton and construction of 5-membered ring[7], (iii) construction of cyclopentane ring system through Michael-Aldol cyclization of appropriate intermediates[8] and

(iv) preparation of requisite substrates from commercially available carbohydrates[9]. It is conceivable that carbohydrates could be ideal precursors for preparing chiral carbocyclic nucleosides. An additional advantage of this approach in using carbohydrates lies in the fact that the optically pure aminocarbocycles are occasionally utilized as potential glycosidase inhibitors and as antibiotics as well.

We had previously shown that chiral carbocycles of different ring sizes[10] fused to furanose ring could be constructed through the application of intramolecular nitrone cycloaddition reaction on glucose-derived nitrones. As a part of our programme in search of analogues of newer chiral carbocyclic nucleosides, we wish to report herein the useful conversion of these furanocarbocycles towards the synthesis of such nucleosides with five-, six- and seven-membered carbocyclic rings.

Results and Discussion

The successful synthesis of optically active functionalized carbocycles[10] by the application of intramolecular nitrone cycloaddition reaction between C-5 nitrone and C-3 olefin (glucose numbering) prompted us to extend our work towards the synthesis of carbocyclic nucleosides **10-16** as shown in Scheme 1. Thus, removal of 1, 2-*O*-isopropylidene groups of **1-3** under acidic conditions followed by vicinal diol cleavage[11] with $NaIO_4$ in aqueous EtOH and reduction with $NaBH_4$ provided the corresponding isoxazolidinocarbocycle derivatives **4-6** in good yields (58-71%). Hydrogenolysis of **4-6** with Pd/C (10%)/cyclohexene[12] cleaved the isoxazolidine rings to afford the respective crude trihydroxy aminocyclopentane derivatives, which without further purification were coupled with 5-amino-4, 6-dichloropyrimidine to provide diamino-chloropyrimidine compounds **7-9** (75-80%). Treatment of **7** with $HC(OEt)_3$/*p*-TSA in DMF at a temperature of 20^{o}C furnished the unexpected 6-dimethylamino-, and 6-methoxy-purine carbocyclic nucleosides **10** (25%) and **11** (21%). Under similar condition, **8** afforded **12** (24%) and **13** (20%), but **9** yielded **14** (19%) and **15** (32%). Ammonolysis of **14** in MeOH cleanly furnished **16** in good yield.



[a] Reagents: (a) 4% H_2SO_4, MeCN, H_2O, rt; (b) $NaIO_4$ (1.9 equiv), EtOH, H_2O, 0°C; (c) $NaBH_4$, MeOH, 10°C; (d) 10% Pd/C,cyclohexene, EtOH, reflux; (e) 5-amino-4, 6-dichloropyrimidine, *n*-BuOH, Et_3N, reflux, (f) $HC(OEt)_3$, *p*-TSA, DMF, 20°C; (g) NH_3, MeOH, 80°C, sealed tube

Scheme 1

In the cyclization reaction the presumed chloropurine derivatives generated *in situ* underwent facile transformation to the respective dimethylaminopurine nucleosides **10**, **12** and **15** conceivably through nucleophilic displacement of the chloro group by dimethylamine derived from DMF. The formation of these products may be due to H-bonding between N-3 of purine

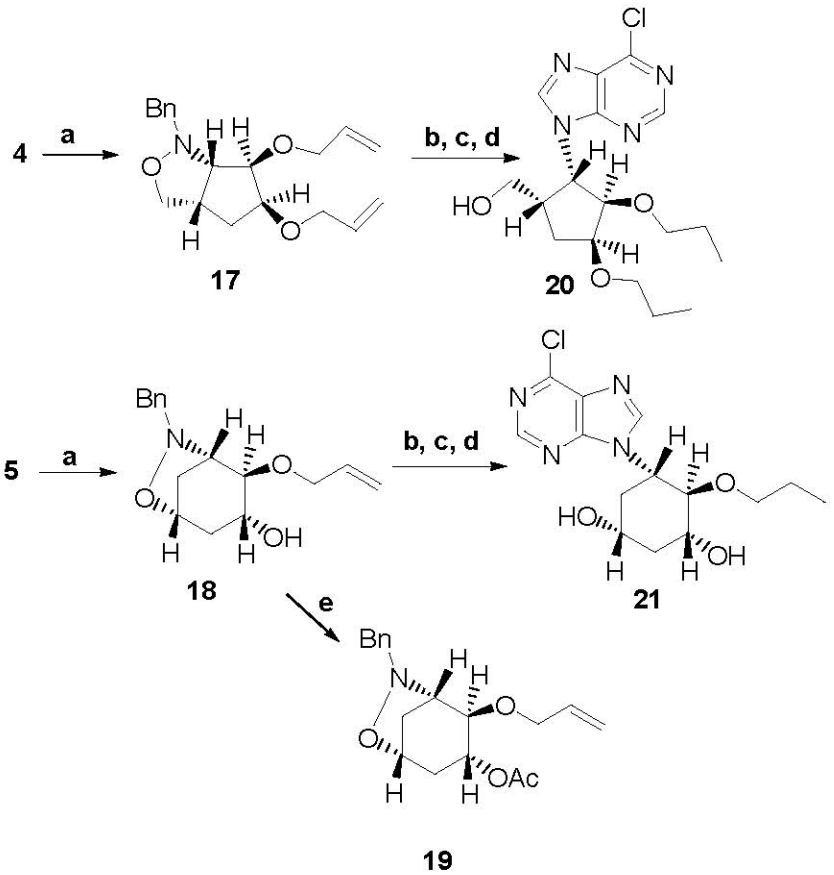
ring and a hydroxy substituent at C-2′ facilitating nucleophilic attack at C-6 by nucleophiles. The minor products **11** and **13** were found to be methoxypurine analogues, which were formed during purification of nucleosides by reversed phase HPLC using H_2O-MeOH solvent system. The chloronucleoside **14** was, however, unchanged during chromatography and in this case no methoxypurine nucleoside was isolated.

To find out the possible role of the hydroxyl group adjacent to the amino group in influencing the ease of substitution of chloro group by NMe_2 and methoxy groups, we wanted to protect the 2′-hydroxyl groups in **4** and **5**. While **4** was easily diallylated to **17**, attempted diallylation of the hydroxyl groups in **5** furnished only the monoallylated derivative **18** presumably due to steric hindrance offered by the bridged ring. The compounds **17** and **18** on transfer hydrogenolysis with cyclohexene-Pd/C treatment furnished crude di-*n*-propyl aminocyclopentane carbocycles, which on cyclization by the usual method furnished only the chloronucleoside analogues **20** and **21** (Scheme 2).

Removal of the acetonide functionality from each of the compounds **1-3** by acid treatment was evident from the disappearance of two distinctive methyl signals at δ ~ 1.30 and 1.50. The generation of two hydroxyl groups in **4-6** was confirmed after their conversion into diacetates. In each case two acetoxy methyl peaks at ~ δ 2.1-2.2 were observed in their ^{1}H NMR spectra. The *trans*-disposition of the 2,3- hydroxyl groups in **5** and **6** was indicated by the recovery of the starting diols from attempted periodate oxidation. However, the same periodate oxidation reaction on **4** resulted in the formation of a dialdehyde characterized by the peak at 1730 cm^{-1} in the IR spectrum of the crude product indicating the cleavage of the cyclopentane ring. During the reaction sequences, the isoxazolidine ring was not disturbed as was evident from the presence of aromatic and benzylic protons in the ^{1}H NMR spectra of the compounds. However, the absence of aromatic as well as benzylic proton signals in the ^{1}H NMR spectra of the crude products obtained by hydrogenolysis of **4-6** suggested the cleavage of the isoxazolidine rings accompanied by debenzylation.

Formation of the products **7-9** from the coupling reactions of the aminocarbocycles with 5-amino-4, 6-dichloropyrimidine was evident from the appearance of a one-proton singlet at δ ~7.8 in the ^{1}H NMR spectrum which is characteristic for the aromatic H-2. On cyclization, the two aromatic proton singlets appeared at δ ~8.1-8.5 in all the purine nucleosides. The characteristic feature in the ^{1}H NMR spectrum (in DMSO-d_6) of the compounds **10, 12** and **15** was the presence of a very broad signal at δ ~3.45 assigned to NMe_2. At 60^{0}C the broad peak changed to a sharp singlet. Additionally, the ^{13}C signal for NMe_2 of these compounds (in DMSO-d_6) could not be detected at normal temperature but appeared as a sharp singlet at δ ~38.8 at an elevated temperature (60^{0}C). The ^{1}H NMR spectrum of **11** and **13** exhibited a sharp singlet at δ 4.10, characteristic for the OCH_3, in addition to the aromatic proton signals at δ 8.39 and 8.51 (for **11**) and 8.36 and 8.50 (for **13**). The presence of ^{13}C peaks at δ ~53.8 (OMe), 143.3, 151.0 (aromatic *CH*) in addition to other appropriate signals are also in conformity with the assigned structures. The mass spectra (FABMS) of **14** and **16** exhibited molecular ion peaks at *m/z* 299 and 301 (for **14**) and at 280 (for **16**).

The ^{1}H NMR signals of the two methylene groups of the compound **18** appeared at δ 1.74, 2.06 and 2.36; N-C*H* (isoxazolidine ring juncture) as well as C*H*-O allyl signals were found at δ 3.61, C*H*-O (isoxazolidine ring juncture) signal at δ 4.58 and C*H*-OH signal at δ 4.65. In confirmation, the proton signal at δ 4.65 shifted downfield to δ 4.85 after acetylation. Finally, upon irradiation of the signal at δ 4.85 of the acetylated product **19,** the doublet of a double doublet (ddd) at δ 2.02 (*J* =15, 7, 2.5 Hz) for one of the methylene protons changed to a broad doublet (*J* =16 Hz). Similarly, upon irradiation of the peak at δ 4.58, the same methylene signal appeared as dd (*J* =7, 15 Hz), confirming the substitution pattern.



[a] Reagents: (a) allyl Br, $Bu_4N^+ Br^-$, 50% NaOH, benzene; (b) 10% Pd/C, cyclohexene, EtOH, reflux, N_2; (c) 5-amino-4, 6-dichloropyrimidine, n-BuOH, Et_3N, reflux; (d) $HC(OEt)_3$, p-TSA, DMF, 20°C; (e) Ac_2O, py, rt, 12 h

Scheme 2

The ^{1}H NMR spectrum of **20** did not show any signal for NMe_2 group and the FABMS showed the molecular ion peak at *m/z* 369 (MH^+ for Cl^{35}) and 371 (MH^+ for Cl^{37}). Similar results were obtained with the nucleoside **21** (protonated molecular ion peaks at *m/z* 327 and 329). Thus, the participation of 2′-OH group in generating dimethylaminopurine and methoxypurine

nucleoside analogues through nucleophilic displacement of chloro group is obvious.

In conclusion, the present work mainly deals with an efficient synthetic route to enantiomerically pure carbocyclic nucleoside analogues with five-, six- and seven-membered rings starting from D-glucose derived precursors. The neighbouring 2′-OH group is involved in forming hydrogen bond with N-3 of purine nucleus and helps to displace C-6 chloro group by nucleophiles like dimethyl amino and methoxy groups.

Experimental Section

General Procedures. Melting points were taken in open capillaries and are uncorrected. IR spectra were measured on a JASCO 700 spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured either on a JEOL FX-100 or on a Bruker AM 300 L spectrometer using TMS as internal standard. Mass spectra were obtained using a JEOL AX-500 spectrometer operating at 70 eV. Optical rotations were measured in a JASCO DIP 360 polarimeter. HPLC was performed on μ Bondapak$^{TM}C_{18}$ column (7.8x300 mm). Flash chromatography was carried out on LiChroprep^{R} RP-18 (Merck).

Preparation of (3*aS*, 5*S*, 6*R*, 6*aR*)-1-benzyl-hexahydrocyclopenta[*c*] isoxazole-5, 6-diol (4). Compound **1** (500 mg, 1.5 mmol) was stirred with 4% H_2SO_4 in CH_3CN-H_2O (3:1, 30 mL) for 24 h at rt. After the completion of the reaction, the solution was neutralized with solid $CaCO_3$, filtered, dried over anhydrous Na_2SO_4 and evaporated to a thick colourless liquid (400mg). This was dissolved in EtOH (25 mL) and cooled to 0^{o}C. An aqueous solution (25 mL) of $NaIO_4$ (555 mg, 2.6 mmol, 1.9 equiv) was added to this solution dropwise with vigorous stirring. After 40 min of stirring, the mixture was filtered, the filtrate was evaporated, and the residue was dissolved in $CHCl_3$ (100 mL). The $CHCl_3$ solution was washed with H_2O (2x40 mL) and dried (Na_2SO_4); evaporation of the solvent afforded a crude ketone (IR 1770 cm^{-1}).

To this ketone dissolved in MeOH (40 mL) at 10^{o}C was added $NaBH_4$ (2x125 mg) portionwise and the mixture was stirred for 5 h. The solvent was evaporated, brine (20 mL) was added to the residue, and the crude product was extracted with $CHCl_3$ (2x50 mL). The combined $CHCl_3$ extract was washed with H_2O (2x25 mL), dried with anhydrous Na_2SO_4 and evaporated to give a residue, which was purified by column chromatography, eluting with $CHCl_3$-MeOH (98:2) mixture to afford **4** (257 mg, 71%): mp 127-128^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.62 (m, 1H), 2.29 (m, 1H), 2.42 (br signal, 1H), 3.14 (m, 1H), 3.34 (brdd, 1H), 3.67 (brdd, 1H), 3.87 (m, 3H), 4.02 (d, 1H, *J*= 13.0 Hz), 4.15 (t, 1H, *J* =8.0 Hz), 7.26 -7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.9, 43.1, 60.4, 72.7, 75.9, 77.3, 80.2, 127.7, 128.5 (2C), 129.1(2C), 136.5; EIMS, *m/z*: 235 (M^{+}). Anal. Calcd for C_{13} $H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95 Found: C, 65.98; H, 7.20; N, 5.13.

Preparation of (1*S*, 2*R*, 3*R*, 5*R*)- 7-benzyl-6-oxa-7-aza-bicyclo [3.2.1] octane-2, 3-diol (5). The compound **5** (in 64% yield) was prepared following the method as used in the preparation of

4 using the same protocol.

5. mp 131-133°C; $[\alpha]_D^{20}$ – 138.0°(*c* 0.23, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.78 (dd, 1H, *J*= 14.7, 5.3 Hz), 1.97-2.08 (m, 2H), 2.35 (brs, 1H), 2.40 (d, 1H, *J* = 11.6 Hz), 3.57 (t, 1H, *J* = 5 Hz), 3.62 (brd, 1H), 3.76 (d, 1H, *J* =13.0 Hz), 3.95 (brd, 1H), 4.13 (d, 1H, *J* = 13.0 Hz), 4.66 (t, 1H, *J* = 5.0 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.8, 35.8, 62.9, 64.1, 71.8, 71.9, 76.6, 127.6, 128.5 (2C), 128.9 (2C), 136.8; EIMS, *m/z*: 235 (M^+).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95 Found: C, 66.18; H, 7.25; N, 5.92.

(1*R*, 2*R*, 3*R*, 5*R*)-8-Benzyl-5, 7-(epoxyimino) cycloheptane-1, 2-diol (6). Compound **3** (1.25 g, 3.36 mmol) was converted to the isoxazolidinocycloheptanediol **6** (520 mg, 58%) according to the method described in the preparation of **4**.

6. thick oil; $[\alpha]^{25}_D$ +36.7° (*c* 0.36, MeOH); ^{1}H NMR ($CDCl_3$+ D_2O, 100 MHz): δ 1.48-2.20 (2xm, 5H), 2.24-2.64 (m, 1H), 3.32-4.12 (m, 7H, consisting of 2xd, 1H each, δ 3.74 and 4.00, *J* = 13 Hz each; t, 1H, δ 3.40, *J*= 4 Hz; dd, 1H, δ 3.55, *J* = 4, 8 Hz; m, 1H, δ 3.75), 4.60 (brd, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 25 MHz): δ 24.9, 28.4, 29.8, 63.1, 67.1, 71.6, 72.0, 76.6, 127.1, 128.0, 128.5, 136.6; FABMS, *m/z*: 250 (M^++1). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.45; H, 7.65; N, 5.25.

Preparation of (1*S*, 2*R*, 3*S*, 4*S*)-3-(5-amino-6-chloro-pyrimidin-4-ylamino)-4-hydroxymethyl-cyclopentane-1, 2-diol (7); (1*R*, 2*R*, 4*R*, 6S)-6-(5-amino-6-chloro-pyrimidin-4-ylamino)-cyclohexane-1, 2, 4-triol (8) and (1*R*, 2*R*, 3*R*, 5*R*)-3-(5-amino-6-chloro-pyrimidin-4-ylamino)-cycloheptane-1,2,5-triol (9). The compound **4** (250 mg, 1.06 mmol, dried over P_2O_5) was dissolved in dry EtOH (30 mL) and heated at reflux after addition of Pd/C (10%, 150 mg) and cyclohexene (3 mL) for 5 h under N_2. The reaction mixture was filtered and evaporated to get a residue, which was dried over P_2O_5. To the residue (150 mg, 1.02 mmol) dissolved in dry *n*-BuOH (25 mL) were added 5-amino- 4, 6-dichloro pyrimidine (250 mg, 1.53 mmol, 1.5 eqv.) and Et_3N (2 mL). The mixture was then heated at reflux for 20 h under N_2 atmosphere. The solvent was evaporated off under reduced pressure to give a solid residue, the aqueous solution of which was washed with chloroform (3x10 mL). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to yield a yellowish solid, which was purified by column chromatography (silica gel). Elution with $CHCl_3$-MeOH (93:7) furnished a pale yellow foamy solid identified as **7** (225 mg, 80%): mp 123-124°C; $[\alpha]_D^{20}$ – 42.3° (*c* 0.23, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.50 (m, 1H), 2.28 (m, 1H), 2.53 (m, 1H), 3.43 (dd, 1H, *J*=11.4, 6.5 Hz), 3.52 (dd, 1H, *J* =11.4, 5.4 Hz), 4.00 (m, 2H), 4.30 (t, 1H, *J* = 8.8 Hz), 7.80 (s, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 31.4, 36.0, 56.2, 61.4, 73.6, 80.0, 122.4, 139.2, 147.3, 153.7; FABMS, *m/z*: 275 (M^++1, for Cl^{35}), 277 (M^++1, for Cl^{37}).

Anal. Calcd for $C_{10}H_{15}ClN_4O_3$: C, 43.72; H, 5.50;N, 20.40. Found: C, 43.12; H, 5.35; N, 19.95.

The compound **8** was prepared from **5** following the procedure as adopted in the preparation of **7** from **4** using the given protocol: **5** (215 mg, 0.91 mmol), dry EtOH (30 mL), Pd/C (10%, 150 mg) and cyclohexene (3 mL) for its conversion to a crude aminocarbocycle (107 mg, 0.72 mmol), then 5-amino- 4, 6-dichloro pyrimidine (177 mg, 1.10 mmol, 1.5 equiv.), Et_3N (2 mL), *n*-BuOH (25 mL) to prepare **8** (158 mg, 80%): pale yellow foam; $[\alpha]_D^{20}$ – 110.6° (*c* 0.21, MeOH).

^{1}H NMR (D_2O, 300 MHz): δ 1.43 (m, 2H), 2.27 (m, 2H), 3.44 (t-like, 1H, *J* = 9.5 Hz), 3.61(m, 1H), 3.88 (m, 1H), 4.03 (m, 1H), 7.84 (s, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 38.1, 39.9, 50.5, 64.2, 69.8, 76.6, 122.4, 139.5, 147.5, 153.5; FABMS, *m/z*: 275 (M^++1, for Cl^{35}), 277 (M^++1, for Cl^{37}). Anal. Calcd for C_{10} H_{15} ClN_4O_3: C, 43.72; H, 5.50;N, 20.40. Found: C, 43.12; H, 5.35; N, 19.95.

The compound **9** was prepared from **6** following the procedure as described in the preparation of **8**.

9. $[\alpha]_D^{20}$ + 40.6^o (*c* 0.25, MeOH); ^{1}H NMR (D_2O, 300 MHz): δ 1.43- 2.25 (m, 5H), 2.43 (m, 1H), 3.44 (t-like, 1H, *J* = 9.5 Hz), 3.61(m, 1H), 3.88 (m, 1H), 4.03 (m, 1H), 7.84 (s, 1H); ^{13}C NMR (D_2O, 75 MHz): δ 32.8, 37.8, 38.9, 50.5, 63.2, 69.5, 75.6, 130.4, 134.5, 145.5, 150.5; FABMS, *m/z*: 291 (M^++1, for Cl^{37}), 289 (M^++1, for Cl^{35}).

Preparation of (1*S*, 2*R*, 3*S*, 4*S*)-3-(6-dimethylamino-purin-9-yl)-4-hydroxymethyl-cyclopentane-1, 2-diol (10) and (1*S*, 2*R*, 3*S*, 4*S*)-4-hydroxymethyl-3-(6-methoxy-purin-9-yl)-cyclopentane-1, 2-diol (11). To the compound **7** (210 mg, 0.76 mmol) dissolved in dry DMF (7 mL) were added *p*-TSA (215 mg, 1.14 mmol) and freshly distilled $CH(OEt)_3$ (2mL) and the reaction mixture was stirred for 24 h at room temperature under N_2. The solvent DMF was evaporated under vacuum, the residue was dissolved in MeOH and the solution was treated with Dowex (OH^-) for 5 h. It was filtered and the filtrate was evaporated to give a solid material, which was subjected to flash chromatography using reverse phase material (LiChroprep) as stationary phase. TLC showed two overlapping compounds, which were finally separated by HPLC using isocratic solution of H_2O-MeOH (9:1) to furnish the purine nucleoside analogues **10** (56 mg, 25 %) and **11** (44 mg, 21%).

10. mp 138-139^{0}C; $[\alpha]_D^{20}$ +65.7^0 (*c* 0.25, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.62 (m, 1H), 2.11 (m, 1H), 2.45 (m, 1H), 2.96 (2H, brd, changing to d, *J* =5.7 Hz at 60^{o}C), 3.46 (6 H, brs, changing to s at 60^o C), 3.87 (1H, brq, changing to dd, *J* =14.7, 7.7 Hz on D_2O exchange), 4.41 (2H, brs, changing to dd, *J* = 7.3, 9.0 Hz on D_2O exchange), 4.66 (t, 1H, *J* = 9 Hz), 5.16 (brs, 1H, exchangeable), 5.32 (brs, 1H, exchangeable), 8.15 (s, 1H), 8.20 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 32.9, 37.7, 59.9, 60.7, 74.3, 78.5, 119.0, 139.2, 150.9, 151.4, 154.1, one signal merged inside DMSO signal; FABMS, *m/z*: 294 (M^++1). Anal. Calcd for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.88. Found: C, 53.12; H, 6.4; N, 23.02.

11. mp 125-126^{0}C; $[\alpha]_D^{20}$ +61.3^0 (*c* 0.25, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.59 (m, 1H), 2.10 (m, 1H), 2.47 (m, 1H), 3.00 (brs, 2H), 3.87 (1H, brq, changing to dd on D_2O exchange), 4.10 (s, 3H), 4.34 (brs, 1H, exchangeable), 4.46 (1H, brt, changing to t-like on D_2O exchange), 4.72 (t, 1H, *J* = 9.0 Hz), 5.16 (brs, 1H, exchangeable), 5.35 (brs, 1H, exchangeable), 8.39 (s, 1H), 8.51 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 32.9, 37.6, 53.7, 60.4, 60.8, 74.0, 78.5, 120.5, 143.4, 151.0, 152.9, 160.1; FABMS, *m/z*: 281 (M^++1).

Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.12; H, 5.22; N, 19.11.

Preparation of (1*R*, 2*R*, 4*R*, 6*S*)-6-(6-dimethylamino-purin-9-yl)-cyclohexane-1, 2, 4-triol (12) and (1*R*, 2*R*, 4*R*, 6*S*)- 6-(6-methoxy-purin-9-yl)-cyclohexane-1, 2, 4-triol (13). The compounds **12** and **13** were prepared from **8** following the method used in the preparation of the

carbocyclic nucleoside derivatives **10** and **11** using the protocols: compound **8** (150 mg, 0.55 mmol), *p*-TSA (156 mg, 0.82 mmol), $CH(OEt)_3$ (2 mL), DMF (7 mL). Yield: **12** (40 mg, 24%) and **13** (32 mg, 20%).

12. mp 253-255^{0}C; $[\alpha]_D^{20}$ +15.4^0 (*c* 0.24, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.42 (q, 1H, *J* = 12.0 Hz), 2.06 (m, 3H), 3.45 (3H, brs, changing to s at 60^{o}C), 3.68 (1H, br signal, changing to m on D_2O exchange), 3.82 (1H, brt, changing to dd, *J* =10, 9 Hz on D_2O exchange,), 4.21(m, 1H), 4.84, 4.89, 4.93 (3x brd, 1H each, exchangeable), 8.14 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 37.8, 39.6, 42.3, 55.5, 64.2, 70.3, 74.9, 119.6, 139.2, 150.3, 151.1, 154.2; FABMS, *m/z*: 294 (MH^+).Anal. Calcd for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.88. Found: C, 53.00; H, 6.44; N, 23.99.

13. mp 208-209^{0}C; $[\alpha]_D^{20}$ +17.4^0 (*c* 0.22, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.44 (q, 1H, *J* =12 Hz), 2.07 (m, 2H), 2.15 (q, 1H, *J* = 12 Hz), 3.70 (m, 1H), 3.82 (1H, m, changing on D_2O exchange to t-like, *J* =10 Hz), 4.09 (s, 1H), 4.31(m, 1H), 4.88 (m, 1H, exchangeable), 5.00 (brd, exchangeable), 8.36 (s, 1H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6, 75MHz): δ 40.3, 42.3, 53.7, 56.1, 64.2, 70.1, 75.1, 120.9, 143.3, 150.8, 152.1, 160.1; FABMS, *m/z*: 281 (M^++1).
Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.09; H, 5.65; N, 18.32.

Preparation of`(1*R*, 2*R*, 3*R*, 5*R*)- 3-(6-chloro-purin-9-yl)-cycloheptane-1, 2, 5-triol (14), (1*R*, 2*R*, 3*R*, 5*R*)-3-(6-dimethylamino-purin-9-yl)-cycloheptane-1, 2, 5-triol (15) and (1*R*, 2*R*, 3*R*, 5*R*)- 3-(6-amino-purin-9-yl)-cycloheptane-1, 2, 5-triol (16). The compounds **14-16** were prepared from **9** following the same procedure used in the cyclization reaction of **7** using the protocols: **9** (200 mg, 0.7 mmol), *p*-TSA (172 mg, 1 mmol), $HC(OEt)_3$ (3 mL) and DMF (10 mL). Yield: **14** (40 mg, 19 %) and **15** (70 mg, 32 %). The chloro nucleoside **14** (10 mg) was heated in a sealed tube in MeOH saturated with ammonia (5 mL) for 40 h. the tube was cooled, opened up, the solvent was evaporated and the crude product was purified by HPLC.

14. mp 184-186^{o}C; $[\alpha]_D^{20}$ +49.0^0 (*c* 0.20, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.50-1.95 (m, 5H), 2.58 (1H, merged with solvent peak), 3.71 (brs, 1H), 3.85 (m, 2H), 4.75 (m, 3H), 5.23 (s, 1H), 8.68 (s, 1H), 8.78 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 25.0, 32.0, 36.1, 54.2, 66.4, 71.0, 74.3, 127.2, 130.5, 146.3, 148.8, 151.2; FABMS, *m/z*: 299 (M^++1, for Cl^{35}), 301 (M^++1, for Cl^{37}).

15. mp 201-202^{o}C; $[\alpha]_D^{20}$ +44.0^0 (*c* 0.3, MeOH); ^{1} H-NMR (DMSO-d_6 , 300 MHz): δ 1.48 (m, 1H), 1.75 (m, 3H), 1.95 (m, 1H), 2.49 (1H, merged with solvent peak), 3.44 (brs, 6H), 3.65 (m, 1H), 3.79 (brs, 1H), 3.86 (m, 1H), 4.60- 4.66 (m, 2H), 4.69 (d, 1H, *J*= 4.0 Hz), 5.22 (d, 1H, *J*= 4.0 Hz), 8.12 (s, 1H), 8.21 (s, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz): δ 25.9, 32.8, 37.4, 38.7, 53.8, 67.3, 72.3, 75.6, 119.7, 139.3, 150.3, 152.3, 155.1; FABMS, *m/z*: 308 (M^++1).

16. mp 208-210^{o}C; $[\alpha]_D^{20}$ +44.7^0 (*c* 0.41, MeOH); ^{1}H NMR (DMSO-d_6,,300 MHz): δ 1.49 (m, 1H), 1.75 (m, 3H), 1.93 (m, 1H), 2.50 (1H, merged signal), 3.65 (brd, 1H, *J*= 9.0 Hz), 3.85 (m, 2H), 4.57-4.71 (m, 3H), 5.25 (d, 1H, *J*= 4.2 Hz), 7.19 (s, 2H), 8.11 (s, 1H), 8.14 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 25.9, 32.7, 37.4, 53.8, 67.3, 72.3, 75.7, 119.1, 140.4, 149.5, 152.9, 156.8; FABMS, *m/z*: 280 (M^++1).

Preparation of 3a*S*, 5*S*, 6*R*, 6a*S*- 5, 6-bis-allyloxy-1-benzyl-tetrahydro-cyclopent[c]isoxazole (17). Allyl bromide (4 ml) was added to a mixture of **4** (300 mg, 1.3 mmol), 50% NaOH (50 mL), tetra butyl ammonium bromide (41.8 mg, 0.13 mmol) in benzene (50 mL) and the mixture was heated at reflux with vigorous stirring for 3 h. The organic layer was separated, washed with water (3x 15 mL), dried (Na_2SO_4), and evaporated to get a reddish syrupy material, which was purified by column chromatography (silica gel) using pet ether-chloroform (3:7) to afford **17** as a colourless syrup (286 mg, 70%): $[\alpha]_D^{20}$ +38.4^0 (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51 (m, 1H), 2.30 (m, 1H), 3.04 (ddt, 1H, *J*= 16.0, 8.8, 2.6 Hz), 3.40 (m, 1H), 3.63 (dd, 1H, *J*= 2.6, 8.6 Hz,), 3.69-3.73 (m, 2H), 3.74 (d, 1H, *J* =12.8 Hz), 3.85 (ddt, 1H, *J*= 12.8, 5.5, 1.2 Hz) 3.96 – 4.09 (m, 4H), 4.01(d, 1H, *J* =12.8 Hz) 5.08 (ddd, 1H, *J*= 10.3, 3.0, 1.2 Hz), 5.12 (dd, 1H, *J*= 3.2, 1.6 Hz), 5.16 (ddd, 1H, *J*= 7.0, 3.0, 1.5 Hz), 5.25 (ddd, 1H, *J*= 17.0, 3.3, 1.5 Hz), 5.72 – 5.96 (m, 2H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 34.2, 41.7, 60.2, 70.7, 70.9, 71.5, 73.4, 82.4, 87.7, 116.4, 116.5, 127.5, 128.4 (2C), 129.3 (2C), 134.9, 135.2, 137.1; EIMS, *m/z*: 315 (M^+). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99: N, 4.44. Found: C, 72.12; H, 7.69; N, 4.27.

Preparation of (1*S*, 2*R*, 3*R*, 5*R*)-2-allyloxy-7-benzyl-6-oxa-7-aza-bicyclo[3.2.1]octan-3-ol (18). Allylation of the compound **5** (200 mg, 0.85 mmol) was carried out as the method described in the preparation of **17** using allyl bromide (4 ml), 50% NaOH solution (50 mL), and benzene (50 mL).

18. colourless syrup (160 mg, 68%); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.74 (dd, 1H, *J*= 14.6, 5.3 Hz), 2.06 (m, 2H), 2.36 (d, 1H, *J*= 11.6 Hz), 3.61 (m, 2H), 3.78 (d, 1H, *J*= 12.8 Hz, partially overlapped by another signal), 3.98 (2xddt, 2x1H, *J*= 13.0, 5.5, 1.5 Hz), 4.12 (d, 1H, *J*= 12.8 Hz), 4.58 (brs, 1H), 4.65 (t, 1H, *J*= 5.0 Hz), 5.12 (ddd, 1H, *J*= 10.5, 2.7, 1.0 Hz), 5.20 (ddd, 1H, *J*= 17.2, 3.2, 1.6 Hz), 5.84 (m, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 30.4, 36.3, 62.9 (2C), 68.5, 70.4, 76.4, 78.7, 116.9, 127.6, 128.5 (2C), 128.8 (2C), 134.5, and 136.8.

EIMS, m/z: 275 (M^+); Anal. Calcd for $C_{16}H_{21}NO_3$; C, 69.79; H, 7.69; N, 5.09; O, 17.43. Found: C, 69.71; H, 7.55; N, 4.97.

Preparation of (1*S*, 2*R*, 3*R*, 5*R*)-2-allyloxy-7-benzyl-6-oxa-7-azabicyclo[3.2.1]octan-3-yl acetate (19). Compound **18** (12 mg, 0.04 mmol) dissolved in pyridine (4 mL) was acetylated with acetic anhydride (1 mL) at 70^o C for 12 h. Pyridine was distilled off by azeotropic distillation with toluene and the residue was purified by chromatography using pet ether-chloroform (1:1) to afford **19** (6 mg) as a creamy solid: $[\alpha]_D^{20}$ –82.2^o (*c* 0.14 , $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.78 (brd, 1H, *J*= 15.0 Hz), 2.02 (ddd, 1H, *J* =15.0, 7.0, 2.5 Hz), 2.11-2.18 (m, 5H including COC*H*$_3$ signal), 3.45 (t-like, 1H, *J*= 3.5 Hz), 3.53 (brs, 1H), 3.76 (d, 1H, *J*= 13.0 Hz), 4.00 (2xdd, 2x 1H, *J*= 13.0, 5.6 Hz), 4.12 (d, 1H, *J*= 13.0 Hz), 4.56 (m, 1H), 4.85 (m, 1H), 5.10 (d, 1H, *J*= 10.3 Hz), 5.17 (dd, 1H, *J*= 17.0, 1.4 Hz), 5.81 (m, 1H), 7.31 (m, 5H); EIMS, *m/z*: 317 (M^+).

Preparation of (1*S*, 2*S*, 3*R*, 4*S*)-2-(6-chloro-purin-9-yl)-3, 4-dipropoxy-cyclopentyl methanol (20). The nucleoside **20** was obtained from **17** according to the method described earlier.

20. sticky solid (15 mg, 21 %); $[\alpha]_D^{20}$ +12.2^0 (*c* 0.18, MeOH); ^{1}H NMR (CD_3OD, 300 MHz): 0.66 (m, 6H), 1.24 (m, 4H), 1.53 (m, 1H), 2.25 (m, 1H), 2.82 (m, 1H), 3.45 (m, 3H), 3.73 (m, 4H), 4.30 (t, 1H, *J* =9.0 Hz), 8.19 (s, 1H), 8.20 (s, 1H); FABMS, *m*/*z*: 369 (MH^+, for Cl^{35}), 371 (MH^+, for Cl^{37}).

Preparation of (1*R*, 3*R*, 4*R*, 5*S*)- 5-(6-chloro-purin-9-yl)-4-propoxy-cyclohexane-1, 3-diol (21). The compound **18** (160 mg, 0.58 mmol) was converted to **21** (20 mg, 11% in 3 steps) adopting the procedure described in the preparation of the nucleosides **10** and **11** from **4**.
21. ^{1}H NMR (CD_3OD, 300 MHz): 0.68 (t, 3H), 1.38 (m, 2H), 1.50 (m, 1H), 1.70 (m, 2H), 2.41 (m, 1H), 3.57 (m, 3H), 4.00 (m, 1H), 4.45 (t, 1H, *J* =6.0 Hz), 8.18 (s, 1H), 8.24 (s, 1H); FABMS, *m/z*: 327 (MH^+, for Cl^{35}), 329 (MH^+, for Cl^{37}).

Acknowledgements

Financial support from DST (Govt. of India) given to S.B.M. is gratefully acknowledged.

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