Chiral Carbocyclic Nucleosides from D-Glucose: Enantiodivergent Synthesis and One-Pot Entry of Dimethylamino Functionality in the Purine Rings

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Cyclization of appropriately designed enose−nitrones derived from D-glucose, having nitrone at C-5 or C-1 and allylic/homoallylic functionalities at C-3 of the sugar backbone, afforded polyhydroxylated aminocarbocycles which were subsequently used as the precursors for carbocyclic nucleoside analogues (**11**, **13**, **16**, **21**, and **23**). The enantiodirecting synthesis of both the enantiomeric pairs of nucleoside analogues **11** and **13**, **21a** and **23a**, and **21c** and **23c**, has also been demonstrated by judiciously applying intramolecular nitrone cycloaddition (INC) reaction. An interesting observation was that in the cyclization reaction of pyrimidine ring to purine ring in DMF solvent, the substitution of C-6 chloro group with a dimethylamino functionality also occurred spontaneously under mild condition, though similar reactions are reported to occur at higher temperature. The hydrogen bonding between N-3 of the purine ring and an appropriate hydroxy substituent in the carbocycle seems to play a crucial role in this reaction.

The significant bioactivities displayed by many of the nucleoside analogues[1] have directed considerable attention toward the synthesis of these compounds. In particular, the compounds derived from the replacement of the oxygen in the furanose ring of a normal nucleoside by a carbon, resulting in the respective carbocyclic analogues,[2] exhibit greater stability against enzymes[3] that cleave the glycosidic linkage of the former. The remarkable antitumor and anti-HIV activities shown by the carbocyclic nucleosides,[4] such as aristeromycin (**1**),[2j] neplanocin A (**2**),[1f] carbovir (**3**),[4j] carboxetanocin G (**4**),[4a]

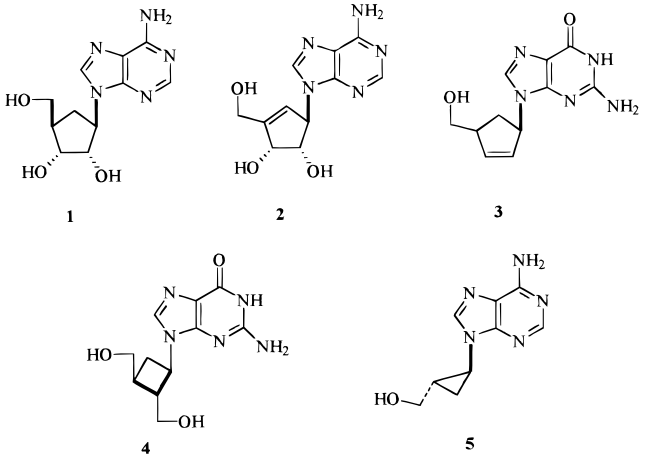

Figure 1.

and cyclopropane nucleoside (**5**)[4k] (Figure 1), have led to intensive search for newer compounds through modification of both the heterocyclic base as well as the sugar moieties of the nucleosides. Moreover, it is highly desirable that the synthetic nucleoside analogues be stereochemically well defined[5] as biological activity of these compounds normally depends on the nature of chirality

(1) (a) Marquez, V. E.; Lim, M.-I. *Med. Res. Rev.* **1986**, *6*, 1. (b) Hobbs, J. B. *Comprehensive Medicinal Chemistry*; Hansch, C. Ed.; Pergamon Press: Oxford, 1990; Vol. 2, pp 306−323. (c) Ohno, M. *Anticancer Agents Based On Natural Product Models, Medicinal Chemistry*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; Vol. 16, pp 73−130. (d) De Clercq, E. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 119. (e) Nair, V.; Jahnke, T. S. *Antimicrob. Agents Chemother.* **1995**, *39*, 1017. (f) Yaginuma, S.; Muto, N.; Tsujino, M.; Sudate, Y.; Hayashi, M.; Ohani, M. *J. Antibiot.* **1981**, *34*, 359.

(2) (a) Ghosh, A.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 6399. (b) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571. (c) Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611. (d) Sundermann, B.; Scharf, H.-D. *Tetrahedron Asymmetry* **1996**, *7*, 1995. (e) Papchikhin, A.; Agback, P.; Plavec, J.; Chattopadhyaya, J. *Tetrahedron* **1995**, *51*, 329. (f) Calvani, F.; Macchia, M.; Rossello, A.; Gismondo, M. R.; Drago, L.; Fassina, M. C.; Cisternino, M.; Domiano, P. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2567. (g) Perigaud, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903. (h) Kikuchi, Y.; Nishiyama, S.; Yamamura, S.; Kato, K.; Fujiwara, S.; Umezawa, K.; Terada, Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1897. (i) Yang, T.-F.; Kim, H.; Kotra, L. P.; Chu, C. K. *Tetrahedron Lett.* **1996**, *37*, 8849. (j) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745. (k) Ranganathan, S.; George, K. S. *Tetrahedron* **1997**, *53*, 3347. (l) Burlina, F.; Fabre, A.; Fourrey, J.-L.; Thomas, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 247. (m) Toyota, A.; Aizawa, M.; Habutani, C.; Katagiri, N.; Kaneko, C. *Tetrahedron* **1995**, *51*, 8783. (n) Vogt, P. F.; Hansel, J.-G.; Miller, M. J. *Tetrahedron Lett.* **1997**, *38*, 2803. (o) Wang, P.; Agrofoglio, L. A.; Newton, M. G.; Chu, C. K.; *Tetrahedron Lett.* **1997**, *38*, 4207. (p) Altman, K.-H.; Bévierre, M.-O.; Mesmaeker, A. D.; Moser, H. F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 431. (q) Díaz, M.; Ortuño, R. M.; *Tetrahedron Asymmetry* **1997**, *8*, 3421. (r) Seley, K. L.; Schneller, S. W.; De Clercq, E. *J. Org. Chem.* **1997**, *62*, 5645. (s) Wang, J.; Busson, R.; Blaton, N.; Rozenski, J.; Herdewijn, P. *J. Org. Chem.* **1998**, *63*, 3051.

(3) Desgranges, C.; Razaka, G.; Rabaud, M.; Bricaud, H.; Balzarini, J.; DeClercq, E. *Biochem. Pharmacol.* **1983**, 3583.

(4) (a) Slusarchyk, W.; Bisacchi, G. S.; Field, A. K.; Hockstein, D. R.; Jacobs, G. A.; McGeever-Rubin, B.; Tino, J. A.; Tuomari, A. V.; Yamanaka, G. A.; Young, M. G.; Zahler, R.; *J. Med. Chem.* **1992**, *35*, 1799. (b) Ishigami, S.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2407. (c) Booth, B. L.; Eastwood, P. R.; *J. Chem. Soc., Perkin Trans. 1* **1995**, 669. (d) Kaiwar, V.; Reese, C. B.; Gray; E. J.; Neidle, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2281. (e) Gharbaoui, T.; Legraverend, M.; Ludwig, O.; Bisagni, E.; Aubertin, A. M.; Chertanova, L. *Tetrahedron* **1995**, *51*, 1641. (f) Mevellec, L.; Huet, F. *Tetrahedron* **1997**, *53*, 5797. (g) Zhao, Y.; Yang, T.; Lee, M.; Lee, D.; Newton, M. G.; Chu, C. K. *J. Org. Chem.* **1995**, *60*, 5236. (h) Lee, M.; Lee, D.; Zhao, Y.; Newton, M. G.; Chun, M. W.; Chu, C. K. *Tetrahedron Lett.* **1995**, *36*, 3499. (i) Rosenquist, A.; Kvarnstrom, I.; Classon, B.; Samuelsson, B. *J. Org. Chem.* **1996**, *61*, 6282. (j) Vince, R.; Hua, M. *J. Med. Chem.* **1990**, *33*, 17. (k) Csuk, R.; von Scholz, Y. *Tetrahedron* **1995**, *51*, 7193.

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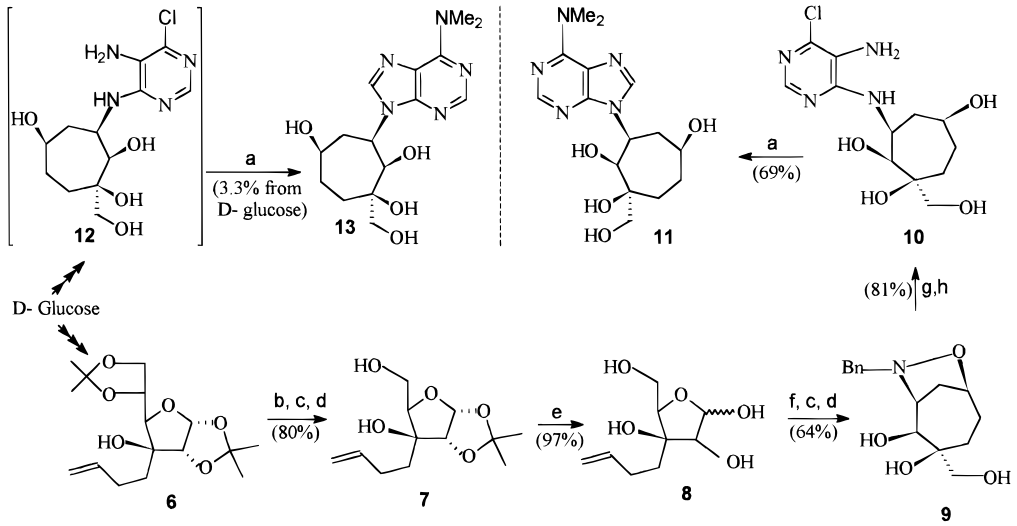
Scheme 1[a]



[a] Reagents: (a) $HC(OEt)_3$, *p*-TSA, DMF, 20 °C; (b) HOAc:H_2O (1:1), 60 °C; (c) $NaIO_4$, EtOH, H_2O; (d) $NaBH_4$, MeOH; (e) 4% H_2SO_4, dioxane, H_2O; (f) BnNHOH, 2-fluoroethanol, rt; (g) 10% Pd/C, cyclohexene, EtOH, reflux; (h) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux.

at the optically active centers. In the previous paper we described a simple procedure for the enantioselective synthesis of a seven-membered carbocyclic nucleoside[6] analogue using readily accessible precursors from D-glucose through an intramolecular nitrone cycloaddition reaction (INC). In a more versatile endeavor toward the extension of this methodology for realizing the synthesis of both the pure enantiomers of a nucleoside analogue incorporating five- and seven-membered carbocyclic rings, we envisioned to achieve the goal through INC reaction[7,8] of appropriately designed enose−nitrones from D-glucose, having nitrone functionality at C-5 or C-1 with the olefin at C-3 (Figure 2). The success of such a scheme, however, hinged upon the mode of the cycloaddition leading to the desired stereochemistry at the newly generated chiral center at the ring junction. We report herein in detail the realization of this objective of enantiodirecting synthesis leading to a simple and efficient route to nucleoside analogues with five- and seven-membered carbocyclic rings, along with an interesting one-pot synthesis of (dimethylamino)purine nucleoside derivatives.

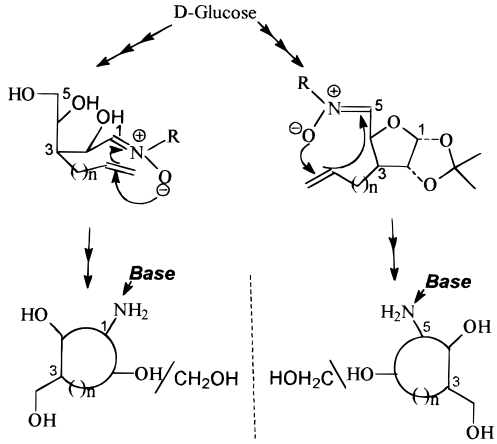


Figure 2. A general presentation for the preparation of enantiomeric pair of carbocyclic nucleosides through INC reaction.

Results and Discussion

The synthesis of polyhydroxylated aminocarbocycle precursors and their transformation to the carbocyclic nucleosides **11**, **13**, **16a−c**, **21a**, **21c**, **23a**, and **23c** (of which **11** and **13**, **21a** and **23a**, and **21c** and **23c** represent enantiomeric pairs) are presented in Schemes 1−3. The successful synthesis of a seven-membered carbocyclic nucleoside analogue **13** by the application of INC reaction between C-5 nitrone and C-3 olefin (glucose numbering) prompted us to extend the process to its enantiomer by taking advantage of the latent C-1 aldehyde and C-3 olefin functionality. Thus, selective removal of the 5,6-*O*-isopropylidene group of **6**[9] (Scheme 1) under mild acidic conditions followed successively by vicinal diol cleavage with $NaIO_4$ and reduction with $NaBH_4$ provided compound **7** in excellent yield (80%). Next, opening of the 1,2-*O*-isopropylidene group with dilute H_2SO_4 furnished tetraol **8** which was directly reacted with BnNHOH in EtOH to form the corresponding C-1 nitrone. Although the attempted cyclization of the nitrone at the double bond of the homoallylic functionality at C-3 failed using various solvents and reaction conditions, the desired

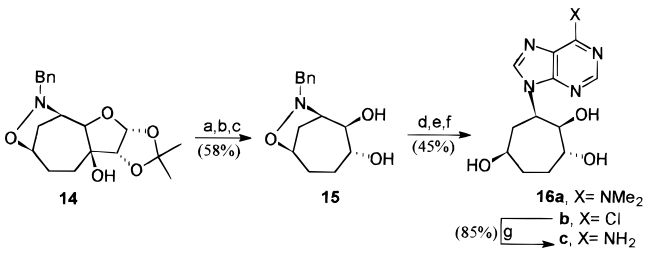
(5) (a) Borth, A. D.; Butt, S.; Biggadike, K.; Exall, A. M.; Roberts, S. M.; Youds, P. M.; Kirk, B. E.; Booth, B. R.; Cameron, J. M.; Cox, S. W.; Marr, C. L. P.; Shill, M. D. *J. Chem. Soc., Chem. Commun.* **1988**, 656. (b) Herdewijn, P.; Balzarini, J.; De Clercq, E.; Vanderhaeghe, H. *J. Med. Chem.* **1985**, *28*, 1385. (c) Ikbal, M.; Cerecau, C.; Le Goffic, F.; Sicsic, S. *Eur. J. Med. Chem.* 1**989**, *24*, 415.

(6) Bar, N. C.; Roy, A.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1997**, *62*, 8948 [In Scheme 2 of this paper one of the reagents was omitted by mistake. Now the reagent is included: (f) $HC(OEt)_3$, *p*-TSA, DMF, 32−35 °C, 24 h].

(7) (a) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis, Novel Strategies in Synthesis*; VCH: New York, 1988. (b) Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990. (c) Hassner, A.; Maurya, R.; Mesko, E. *Tetrahedron Lett.* **1988**, *29*, 5313. (d) Shing, T. K. M.; Elsley, D. A.; Gillhouley, J. G. *J. Chem. Soc., Chem. Commun.* **1989**, 1280. (e) Peet, N. P.; Huber, E. W.; Farr, R. A. *Tetrahedron* **1991**, *47*, 7537. (f) Duclos, O.; Dureault, A.; Depezay, J. C. *Tetrahedron Lett.* **1992**, *33*, 1059. (g) Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett.* **1990**, *31*, 1171. (h) Ferrier, R. J.; Prasit, P. *J. Chem. Soc., Chem. Commun.* **1981**, 983. (i) Farr, R. A.; Peet, N. P.; Kang, M. S. *Tetrahedron Lett.* **1990**, *31*, 7109. (j) Nakata, M.; Akazawa, S.; Kitamura, S.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 5363. (k) Bhattacharjee, A.; Bhattacharjya, A.; Patra, A. *Tetrahedron Lett.* **1995**, *36*, 4677.

(8) Collins, P. M.; Ashwood, M. S.; Eder, H.; Wright, S. H. B.; Kennedy, D. J. *Tetrahedron Lett.* **1990**, *31*, 2055.

Scheme 2[a]



[a] Reagents: (a) 4% H_2SO_4, MeCN, H_2O, rt; (b) $NaIO_4$ (2.2 equiv), EtOH, H_2O, 10 °C; (c) $NaBH_4$, MeOH, 10 °C; (d) 10% Pd/C, cyclohexene, EtOH, reflux; (e) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux; (f) $HC(OEt)_3$, *p*-TSA, DMF, 20 °C; (g) NH_3, MeOH, 80 °C, sealed tube.

transformation could finally be achieved in 2-fluoroethanol as the reaction solvent. The cyclized product was directly transformed to the isoxazolidinocarbocycle **9** (62%) through sequential treatments with $NaIO_4$ (1.2 equiv) and $NaBH_4$. Hydrogenolysis of **9** with Pd/C (10%)/cyclohexene[8] afforded a tetrahydroxy aminocarbocycle derivative which was then coupled with 5-amino-4,6-dichloropyrimidine to provide the diaminopyrimidine compound **10** (81%). Treatment of **10** with $HC(OEt)_3$/*p*-TSA in DMF at a lower temperature (18−20 °C) than reported earlier[6] furnished an unexpected 6-(dimethylamino)purine carbocyclic nucleoside analogue **11** (69% yield). Similar treatment of **12**[6] also afforded **13** (63%). The two enantiomeric compounds **11** and **13** exhibited superimposable ^{1}H NMR, ^{13}C NMR, and IR spectra as well as optical rotations of equal magnitude but opposite sign, confirming their assigned stereostructures.

The isoxazolidine **14**, obtained in eight steps[9] from D-glucose, furnished **15** (58%) through a sequence of reactions (Scheme 2) involving opening of isopropylidene protection with dilute H_2SO_4 and cleavage of resulting triol with $NaIO_4$ (2.2 equiv) followed by $NaBH_4$ reduction. The relative trans disposition of the 2,3-hydroxyl groups was indicated by the recovery of diol **15** from attempted periodate oxidation, presumably due to nonformation of the cyclic intermediate for the cleavage reaction. Opening up of the isoxazolidine ring followed by coupling with 5-amino-4,6-dichloropyrimidine and application of the usual ring closure reaction smoothly converted the isoxazolidine **15** to the carbocyclic nucleoside analogues **16a** and **16b** in the ratio of 8:1 (Scheme 2). Ammonolysis[10] of **16b** in MeOH furnished **16c** in good yield.

In an analogous manner (Scheme 3), the enantiomerically pure five-membered isoxazolidino-carbocycles **17** and **18**, obtained from D-glucose via similar routes,[6] were subjected to transfer hydrogenolysis (Pd/C,cyclohexene) furnishing the enantiomeric pairs of tetrahydroxy aminocyclopentane derivatives **19** ($[\alpha]_D$ +10.5°) and **22** ($[\alpha]_D$ −10.8°). Each of the amines **19** and **22**, on coupling with 5-amino-4,6-dichloropyrimidine and subsequent ring closure with $HC(OEt)_3$ in DMF in the presence of *p*-TSA followed by chromatography on silica gel using $CHCl_3$−MeOH (9:1) as eluent, gave the desired enantiomerically pure (dimethylamino)purine nucleoside analogues **21a** and **23a** in 50−53% yields. The minor products isolated from the chromatography were proved to be the respective enantiomeric pairs of methoxypurine analogues **21c** and **23c**, presumably resulting from the displacement of chloro group from the compounds **21b** and **23b**. Attempted isolation of the chloro intermediates even by reversed phase HPLC (H_2O−MeOH, 9:1) failed, yielding only the respective methoxy-substituted analogues instead. The chloronucleoside **16b** was, however, unchanged, and isolated by chromatography.

All the in situ generated chloropurine derivatives underwent facile transformation to the respective (dimethylamino)purines **11**, **13**, **16a**, **21a**, and **23a**, conceivably through nucleophilic displacement of the chloro group by dimethylamine derived from DMF. However, similar nucleophilic substitutions of aromatic chloro compounds in DMF are reported to require higher temperature.[11] The possibility of hydrogen bonding between N-3 and 2′-OH causing the formation of a partial positive charge on the N atom and thereby increasing the electrophillicity at C-6 cannot be ruled out.

The structure of the isoxazolidine **9** was based upon the appearance of a one-proton doublet at δ 2.06 and a one-proton doublet of a triplet at δ 2.44 in its ^{1}H NMR spectrum as well as an upfield triplet at δ 29.4 in its ^{13}C NMR spectrum assigned to the bridge methylene group. The enantiomeric nature of the compounds **11** ($[\alpha]_D$ −34.1°) and **13** ($[\alpha]_D$ +34.2°) was clearly established by their superimposable ^{1}H NMR, ^{13}C NMR, and IR spectra as well as from their optical rotations. Similarly, both the pair of enantiomers **21a** ($[\alpha]_D$ +36.8°) and **23a** ($[\alpha]_D$ −36.2°), and **21c** ($[\alpha]_D$ +51.6°) and **23c** ($[\alpha]_D$ −51.0°), generated from D-glucose had comparable spectral data and optical rotations.

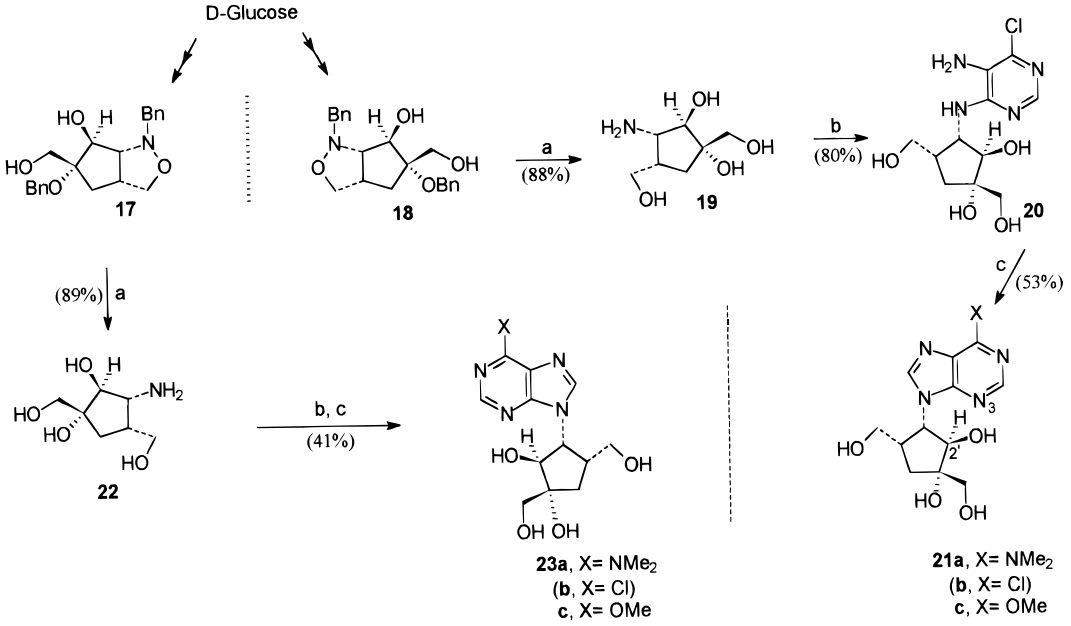
Further, formation of the products from the coupling reactions of the aminocarbocycles with 5-amino-4,6-dichloropyrimidine was evident from the appearance of a one-proton singlet at δ ∼7.8 in the ^{1}H NMR spectrum which is characteristic for the aromatic H-2 proton. On cyclization, the two aromatic proton singlets appeared at δ 8.3−8.5 in the products. The characteristic feature in the ^{1}H NMR spectrum of **21a** (DMSO-d_6) was a very broad signal at δ 3.45 assigned to NMe_2, along with a doublet at δ 4.68 and a triplet at δ 4.85 attributed to H′-2 and H′-1 discernible after addition of D_2O. The aromatic signals at δ 8.16 (two overlapping peaks), 8.183 and 8.188 arise possibly due to the existence of two equilibrium forms. At 60 °C (in DMSO-d_6), these signals were transformed to two discrete peaks at δ 8.12 and 8.17, and the broad peak assigned to NMe_2 was changed to a sharp singlet due to fast exchange of the two forms. Surprisingly, the ^{13}C signal for NMe_2 of this compound (in DMSO-d_6) could not be discerned at normal temperature but appeared as a sharp singlet at δ 38.8 at elevated temperature (60 °C). A similar spectral behavior was observed in the case of compound **23a**. The ^{1}H NMR spectrum of each of the enantiomeric pairs **21c** and **23c** exhibited a sharp singlet at δ 4.10, a doublet at δ 4.75 and a triplet at δ 4.98, characteristic signals for the OCH_3, H′-2 and H′-1, in addition to the aromatic proton

(9) Patra, R.; Bar, N. C.; Roy, A.; Achari, B.; Ghoshal, N.; Mandal, S. B. *Tetrahedron* **1996**, *52*, 11265.

(10) (a) Yoshikawa, M.; Nakae, T.; Cha, B. C.; Yokokawa, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1989**, *37*, 545. (b) Kitagawa, I.; Cha, B. C.; Nakae, T.; Okaichi, Y.; Takinami, Y.; Yoshikawa, M. *Chem. Pharm. Bull.* **1989**, *37*, 542.

(11) (a) Lord, W. M.; Peters, A. T. *Chem., Ind.* **1973**, 227. (b) Lord, W. M.; Peters, A. T. *J. Chem. Soc. (C)* **1968**, 783. (c) Asquith, R. S.; Lord, W. M.; Peters, A. T.; Wallace, F. *J. Chem. Soc.* (*C*) **1966**, 95. (d) Lunt, E. *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; 1979; pp 515−516.

Scheme 3[a]



[a] Reagents: (a) 10% Pd/C, EtOH, reflux; (b) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux; (c) $HC(OEt)_3$, *p*-TSA, DMF, 20 °C.

signals at δ 8.40 and 8.50. The ^{13}C peaks at δ 60.9, 79.5 and 53.7 are also in conformity with the assigned structures.

The presence of four methylene triplets in the ^{13}C NMR spectrum of **15** clearly indicated the elimination of a two-carbon residue from **14** during oxidative degradation with $NaIO_4$. In the ^1H NMR spectrum of **16a,** a singlet was observed at δ 3.44 assigned to NMe_2, along with the aromatic proton signals at δ 8.16 and 8.24. The four upfield ^{13}C signals for 3 × CH_2 and NMe_2 appeared at δ 25.1, 31.5, 36.5, and 37.7; appropriate spectral profiles were also obtained for compounds **16b** and **16c**.

In conclusion, a short and efficient route toward enantiomerically pure and optically active five- and seven-membered carbocyclic nucleosides has been developed. We have also established a simple method for the preparation of a pair of enantiomers of carbocyclic nucleoside analogues starting with enose−nitrones derived from D-glucose as the chiral source. The present method might be applicable to synthesize both the enantiomers of carbocycles and heterocycles of different ring-sizes. Further, in the cyclization reaction leading to purine ring formation in DMF, the likelihood of hydrogen bonding between N-3 of the purine ring and an appropriate hydroxy substituent on the carbocycle appears to facilitate the substitution of the 6-chloro group with a dimethylamino functionality, providing a one-pot synthetic route to such purine nucleoside analogues.

Experimental Section

General Methods. Melting points are uncorrected. ^1H NMR spectra were determined with a 100 MHz (^{13}C at 25 MHz) or a 300 MHz (^{13}C at 75 MHz) spectrometer using TMS as internal standard. Mass spectra were recorded under electron impact at 70 eV. Reagents and solvents were of analytical grade or were purified by standard procedures prior to use. Column chromatography was performed with silica gel (60−120 mesh; SRL, India). Flash column chromatography was performed with silica gel (230−400 mesh; SRL, India). Thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F_{254} precoated plates. High performance liquid chromatography (HPLC) was done on Waters Associates model 440 instrument using Nova Pak reverse phase C-18 column (particle size 5 μm, column size 3.0 mm × 150 mm).

1,2-*O*-Isopropylidene-3-(but-1-enyl)-α-D-xylofuranose (7). The diisopropylidene compound **6** (2.00 g, 6.37 mmol) dissolved in HOAc−H_2O (1:1) mixture (50 mL) was heated at 60 °C for 45 min. The solvent was evaporated in vacuo, the gummy residue was extracted with $CHCl_3$ (2 × 40 mL), the $CHCl_3$ solution was washed with H_2O (2 × 40 mL) and dried (Na_2SO_4), and the solvent was removed to give a crude material. To this material dissolved in EtOH (25 mL) and cooled to 10 °C was added an aqueous solution (25 mL) of $NaIO_4$ (1.63 g, 7.6 mmol, 1.2 equiv) dropwise with vigorous stirring. After 40 min 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 (2 × 40 mL) and dried (Na_2SO_4); evaporation of the solvent afforded the crude aldehyde (1.58 g) (IR: 1745 cm^{-1}).

To this aldehyde dissolved in MeOH (40 mL) at 10 °C was added $NaBH_4$ (2 × 125 mg) portionwise, and the mixture was stirred for 5 h. The solvent was evaporated, H_2O (25 mL) was added to the residue, and the crude product was extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ solution was washed with H_2O (2 × 25 mL), dried (Na_2SO_4), and evaporated to give a residue which was purified by column chromatography, eluting with $CHCl_3$−MeOH (100:1) mixture to afford **7** (1.25 g, 80%): gum; $[\alpha]^{25}_D$ +40.2° (*c* 0.15, $CHCl_3$); ^1H NMR ($CDCl_3$, 100 MHz) δ 1.36 (s, 3H), 1.58 (s, 3H), 2.12 (m, 2H), 2.44 (m, 2H), 3.84 (d, 2H, J = 6 Hz), 4.32 (t, 1H, J = 6 Hz), 4.38 (brs, 1H, exchangeable), 4.46 (d, 1H, J = 4 Hz), 4.70 (s, 1H, exchangeable), 5.12−5.30 (m, 2H), 5.74 (d, 1H, J = 4 Hz), 5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 26.3, 27.2, 27.9, 31.8, 60.8, 80.8, 83.2, 85.0, 103.5, 112.6, 114.9, 138.7; EIMS, *m/z*: 244 (M^+), 229 (M^+ − 15), 226,186.

3-(But-1-enyl)-α,β-xylofuranose (8). Compound **7** (980 mg, 4 mmol) was dissolved in 4% H_2SO_4 in dioxane−water (35 mL) and stirred at room temperature for 20 h. The solution was neutralized with solid $CaCO_3$ and filtered, and the solvent was evaporated in vacuo to obtain a gummy material which was chromatographed on a silica gel column, eluting with $CHCl_3$−MeOH (9:1) to afford an anomeric mixture of **8** (795 mg, 97%): gum; ^1H NMR (DMSO-d_6 + D_2O) δ 2.42−2.63 (m, merged with solvent peak), 3.92 (brd), 4.32 (brt), 4.42 (d), 4.44 (s), 5.28 (m), 5.72 (d), 5.76 (s), 6.08 (m).

(1*S*,2*S*,5*S*,7*S*)-2-(Hydroxymethyl)-8-benzyl-5,7-(epoxyimino)cycloheptane-1,2-diol (9). The anomeric mixture of xylofuranose **8** (780 mg, 3.82 mmol) in 2-fluoroethanol (30 mL) was treated with BnNHOH (565 mg, 4.6 mmol, 1.2 equiv), and the solution was stirred at room temperature for 48 h. The solvent was evaporated, and the crude mixture on subsequent reaction with $NaIO_4$ (980 mg) and $NaBH_4$(150 mg) following the method described earlier (in the preparation of **7**) afforded a product which was purified by column chromatography on silica gel using $CHCl_3$−MeOH (49:1) mixture as the eluent to furnish **9** (680 mg, 64%): gum; $[\alpha]^{25}_D$ −59.8° (*c* 0.42, MeOH); ^{1}H NMR ($CDCl_3$, 100 MHz) δ 1.24−1.88 (m, 4H), 2.06 (d, 1H, J = 14 Hz), 2.44 (dt, 1H, J = 8, 8, 14 Hz), 3.28 (2H, brs becoming 1H, d, J = 4 Hz on D_2O exchange), 3.42 (3H, m becoming 1H, t, J = 10 Hz on D_2O exchange), 3.58−3.68 (m, 2H), 3.77 (d, 1H, J = 14 Hz), 4.06 (d, 1H, J = 14 Hz), 4.68 (m, 1H), 7.34 (m, 5H); FABMS, *m*/*z*: 280 (M^+ + 1). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58. Found: C, 64.48; H, 7.59.

(1*S*,2*S*,3*S*,5*S*)-3-[(6-Chloro-5-aminopyrimidin-4-yl)amino]-1-(hydroxymethyl)cycloheptane-1,2,5-triol (10). The mixture of isoxazolidinocarbocycle **9** (600 mg, 2.15 mmol), Pd/C (10%, 150 mg), and cyclohexene (7 mL) was heated at reflux under N_2 for 5 h. The Pd−C was filtered off, and the solvent was evaporated in vacuo. The crude free amine, without further purification, was taken in dry *n*-BuOH (25 mL), treated with 5-amino-4,6-dichloropyrimidine (423 mg, 2.58 mmol, 1.2 equiv), and Et_3N (4 mL), and then the mixture was heated at reflux for 20 h under N_2. The solvent was evaporated in vacuo, and the residue was extracted with H_2O (3 × 35 mL). The aqueous part was washed with $CHCl_3$ (2 × 25 mL) and then evaporated to a thick oil. Purification by column chromatography on silica gel and eluting with $CHCl_3$−MeOH (23:1) furnished **10** (554 mg, 81%)) as a foam: $[\alpha]^{25}_D$ + 45.3° (*c* 0.63, MeOH); ^{1}H NMR (DMSO-d_6,100 MHz) δ 1.44−2.48 (m, 6H), 3.60−4.30 (m, 5H), 4.44 (s, 1H, exchangeable), 4.48 (m, 2H, exchangeable), 4.90 (d, 1H, J = 4 Hz, exchangeable), 5.26 (brs, 2H, exchangeable), 6.80 (d, 1H, J = 8 Hz, exchangeable), 7.75 (s, 1H); ^{13}C NMR (D_2O + dioxane, 25 MHz) δ 28.9, 29.8, 36.4, 50.6, 68.6, 70.5, 74.8, 75.4, 123.8, 139.9, 148.1, 153.1; FABMS, *m*/*z*: 319, and 321 (M^+ + 1).

(1′*S*,2′*S*,3′*S*,5′*S*)-9-[1-(Hydroxymethyl)-1,2,5-trihydroxycyclohept-3-yl]-6-(dimethylamino)adenine (11). To the diaminopyrimidine derivative **10** (200 mg, 0.63 mmol) dissolved in freshly distilled dry DMF (7 mL) was added *p*-TSA (144 mg, 0.76 mmol, 1.2 equiv) and $HC(OEt)_3$ (4 mL), and the mixture was stirred at 18−20 °C for 30 h under N_2. The acid was neutralized with Et_3N (0.5 mL), and the solvent was evaporated in vacuo to a gummy residue. This was dissolved in MeOH (2 mL), and the solution was passed through Dowex-1-OH$^-$ resin column. Elution with MeOH (4 × 20 mL) and evaporation of the solvent afforded the impure nucleoside which was further poured onto a Dowex-50W-H$^+$ resin column. Aqueous-NH_3 (20%, 4 × 25 mL) eluted almost pure carbocyclic (dimethylamino)nucleoside, which was again purified by column chromatography on silica gel eluting with $CHCl_3$−MeOH (9:1) mixture to afford **11** (146 mg, 69%): mp 210−212 °C dec; $[\alpha]^{25}_D$ −34.1° (*c* 0.21, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.48−2.10 (m, 5H), 2.48 (m, 1H overlapped with DMSO signal), 3.46 (s, 6H), 3.72 (brd, 2H) 4.40 (s, 1H, exchangeable), 4.76 (m, 3H changing to a brd, 1H, J = 10 Hz on D_2O exchange), 5.32 (d, 1H, J = 5 Hz, exchangeable), 8.12 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 25 MHz) δ 29.8, 30.1, 36.7, 37.8, 52.0, 68.4, 70.1, 72.6, 73.5, 118.8, 138.1, 149.2, 151.4, 154.2; FABMS, *m*/*z*: 338 (M^+ + 1). Anal. Calcd for $C_{15}H_{23}N_5O_4$: C, 53.40; H, 6.87; N, 20.76. Found: C, 53.42; H, 6.64; N, 20.48.

(1′*R*,2′*R*,3′*R*,5′*R*)-9-[1-(Hydroxymethyl)-1,2,5-trihydroxycyclohept-3-yl]-6-(dimethylamino)adenine (13). Crude compound **12**[6] (320 mg) in DMF (10 mL) was treated with $HC(OEt)_3$ and *p*-TSA, following the procedure used in the preparation of **11**, and cyclized to the carbocyclic nucleoside **13** (205 mg, 63%): mp 182−183 °C; $[\alpha]^{25}_D$ +34.2° (*c* 0.36, MeOH); FABMS, *m*/*z*: 338 (M^+ + 1).

(1*R*,2*R*,3*R*,5*R*)-8-Benzyl-5,7-(epoxyimino)cycloheptane-1,2-diol (15). Compound **14** (1.25 g, 3.36 mmol) was converted to the isoxazolidinocycloheptanediol **15** (520 mg, 58%) through the sequence of reactions involving opening of isopropylidene protection with dil H_2SO_4, cleavage of the diol with $NaIO_4$, and $NaBH_4$ reduction according to the method described in the preparation of **9**.

15: 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 (2×m, 5H), 2.24−2.64 (m, 1H), 3.32−4.12 (m, 7H consisting of two doublets at δ 3.74 and 4.00, J = 13 Hz each; 1H triplet at δ 3.40, J = 4 Hz; 1H doublet of a doublet at δ 3.55, J = 4, 8 Hz; 1H multiplet at δ 3.75), 4.60 (brd, 1H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.9 (t), 28.4 (t), 29.8 (t), 63.1 (t), 67.1 (d), 71.6 (d), 72.0 (d), 76.6 (d), 127.1 (d), 128.0 (d), 128.5 (d), 136.6 (s); 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.

(1′*R*,2′*R*,3′*R*,5′*R*)-9-[1,2,5-Trihydroxycyclohept-3-yl]-6-(dimethylamino)adenine (16a) and (1′*R*,2′*R*,3′*R*,5′*R*)-9-[1,2,5-Trihydroxycyclohept-3-yl]-6-chloroadenine (16b). The isoxazolidino-cycloheptane diol **15** (1.25 g, 5 mmol) was hydrogenolyzed with Pd/C (10%, 300 mg) and cyclohexene (15 mL) in EtOH (20 mL) (procedure as adopted with **9**). After evaporation of the solvent, the crude aminocycloheptane triol (780 mg) was coupled with 5-amino-4,6-dichloropyrimidine (840 mg, 5.76 mmol) (similar procedure as adopted in the preparation of **10**). The coupling product was then cyclized, using $HC(OEt)_3$/*p*-TSA, to a mixture of **16a** and **16b** following the procedure used for the preparation of **11**. The two products **16a** and **16b** were purified by column chromatography over silica gel using $CHCl_3$−MeOH (19:1) as the eluent to get **16a** (610 mg, 40%) and **16b** (75 mg, 5%).

16a: mp 201−202 °C dec; $[\alpha]^{25}_D$ +44.0° (*c* 0.3, MeOH); ^{1}H NMR (DMSO-d_6, 100 MHz) δ 1.32−2.20 (m, 5H), 2.50 (1H signal, merged with solvent), 3.44 (s, 6H), 3.60 (br signal, 1H, overlapped by NMe_2 signal), 3.84 (brs, 2H), 4.52−4.88 (m, 3H changing to a brd,1H, J = 12 Hz on D_2O exchange),5.24 (d, 1H, J = 4 Hz, exchangeable), 8.16 (s, 1H), 8.24 (s, 1H); ^{13}C NMR (DMSO-d_6, 25 MHz) δ 25.1 (t), 31.5 (t), 36.5 (t), 37.7 (q), 52.8 (d), 66.4 (d), 71.4 (d), 74.7 (d), 118.8 (s), 138.1 (d), 149.3 (d), 151.2 (d), 154.2 (s); FABMS,*m*/*z*: 324 (M^+ + 1). Anal. Calcd for $C_{14}H_{21}N_5O_3$: C, 52.00; H, 6.55; N, 21.66. Found: C, 52.01; H, 6.45; N, 21.43.

16b: mp 184−186 °C; $[\alpha]^{25}_D$ +49.0° (*c* 0.2, MeOH); ^{1}H NMR (DMSO-d_6, 100 MHz) δ 1.40−2.20 (m, 5H), 2.50 (1H, merged with solvent peak), 3.84 (brs), 4.56−4.92 (m, 3H changing to a brd, 1H, J = 12 Hz on D_2O exchange), 5.16 (d, 1H, J = 4 Hz, exchangeable), 8.70 (s, 1H), 8.82 (s, 1H); ^{13}C NMR (DMSO-d_6, 25 MHz) δ 25.0, 31.7, 36.1, 54.1, 66.4, 71.0, 74.3, 130.4, 134.4, 145.9, 150.9, 151.1; FABMS, *m*/*z*: 315, and 317 (M^+ + 1). Anal. Calcd for $C_{12}H_{15}ClN_4O_3$: C, 45.80; H, 4.80; N, 17.80. Found: C, 45.76; H, 4.82; N, 17.46.

(1′*R*,2′*R*,3′*R*,5′*R*)-9-[1,2,5-Trihydroxycyclohept-3-yl]adenine (16c). Chloroadenine **16b** (65 mg, 0.22 mmol) was dissolved in dry methanolic ammonia solution (5 mL) and heated at 100 °C for 10 h in a sealed tube. Usual workup followed by purification in flash chromatography using 4% methanolic $CHCl_3$ as the eluent furnished **16c** (52 mg, 85%): mp 208−210 °C; $[\alpha]^{25}_D$ +44.7° (*c* 0.41, MeOH); ^{1}H NMR (DMSO-d_6, 100 MHz) δ 1.40−2.20 (m, 5H), 2.51 (m, 1H, overlapped with solvent signal), 3.60 (br signal, 1H), 3.86 (brs, 2H), 4.40−4.90 (m, 3H changing to a brd, 1H, J = 10 Hz on D_2O exchange), 5.25 (br signal,1H, exchangeable), 7.24 (brs, 2H, exchangeable), 8.20 (s, 2H); ^{13}C NMR (DMSO-d_6, 25 MHz) δ 25.1, 31.8, 36.5, 53.2, 66.4, 71.4, 74.8, 118.0, 140.4, 148.4, 150.4, 154.5; FABMS, *m*/*z*: 280 (M^+ + 1). Anal. Calcd for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.14; N, 25.08. Found: C, 51.58; H, 6.08; N, 24.88.

(1*R*,2*R*,3*S*,4*S*)-1,4-Bis(hydroxymethyl)-3-aminocyclopentane-1,2-diol (19), and (1*S*,2*S*,3*R*,4*R*)-1,4-Bis(hydroxymethyl)-3-aminocyclopentane-1,2-diol (22). Compounds **18** (480 mg, 1.35 mmol) and **17** (500 mg, 1.41 mmol) were hydrogenolyzed separately with Pd/C (10%, 800 mg), cyclohexene (4.5 mL), and EtOH (40 mL) to their respective hydroxyaminocyclopentanes **19** (210 mg) and **22** (212 mg) following the procedure used for **9**.

19: $[\alpha]^{25}_D$ +10.5° (*c* 0.34, H_2O); ^{1}H NMR (D_2O + acetone, 300 MHz) δ 1.40 (dd, 1H, J = 7.5, 14.5 Hz), 1.94 (dd, 1H, J =

7.5, 14.5 Hz), 2.27 (m, 1H), 3.11 (t, 1H, $J = 7.5$ Hz), 3.43−3.70 (m, 4H), 3.87 (d, 1H, $J = 7.5$ Hz); ^{13}C NMR (D_2O + acetone, 75 MHz) δ 35.3, 39.2, 58.1, 62.1, 64.7, 80.9, 84.6; FABMS, *m/z*: 178 ($M^+ + 1$).

22: $[\alpha]^{25}_D$ −10.8° (*c* 0.34, H_2O); FABMS, *m/z*: 178 ($M^+ + H$).

(1*S*,2*R*,3*S*,4*S*)-3-(6-Chloro-5-aminopyrimidin-4-yl)amino-1,4-bis(hydroxymethyl)cyclopentane-1,2-diol (20). Compound **19** (210 mg, 1.19 mmol) was coupled with 5-amino-4,6-dichloropyrimidine (293 mg, 1.5 mmol), according to the previous procedure to furnish **20** (290 mg, 80%): foam; $[\alpha]^{25}_D$ +25.7° (*c* 0.34, MeOH); ^{1}H NMR (DMSO-d_6, 100 MHz) δ 1.74 (dd, 1H, $J = 6$, 13 Hz), 2.22 (dd, 1H, $J = 9$, 13 Hz), 3.68−4.68 (m), 4.71 (s, 1H, exchangeable), 4.83 (d, 1H, $J = 6$ Hz, exchangeable), 5.22 (brs, 2H, exchangeable), 6.73 (d, 1H, $J = 8$ Hz, exchangeable), 7.78 (s, 1H); ^{13}C NMR (DMSO-d_6, 25 MHz) δ 35.2, 37.5, 53.9, 61.4, 62.6, 77.6, 79.4, 123.6, 139.8, 148.2, 153.2; FABMS, *m/z*: 305, and 307 ($M^+ + 1$).

(1′*S*,2′*R*,3′*S*,4′*S*)-9-[1,4-Bis(hydroxymethyl)-1,2-dihydroxycyclopent-3-yl]-6-dimethylaminoadenine (21a) and (1′*S*,2′*R*,3′*S*,4′*S*)-9-[1,4-Bis(hydroxymethyl)-1,2-dihydroxycyclopent-3-yl]-6-methoxyadenine (21c). The diaminopyrimidine derivative **20** (280 mg, 0.92 mmol) was treated with $HC(OEt)_3$/*p*-TSA following the method adopted with compound **10**. Usual workup and purification (as in the preparation of **11)** afforded a mixture of **21a** and **21c** which was purified on HPLC using H_2O−MeOH (9:1) at a flow rate of 1 mL/min to afford pure **21a** (148 mg, 50%) and **21c** (9 mg, 3%).

21a: sticky gum; $[\alpha]^{25}_D$ +36.8° (*c* 0.37, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O, 300 MHz) δ 1.71 (dd, 1H, $J = 6$, 13.5 Hz), 2.22 (dd, 1H, $J = 9$, 13.5 Hz), 2.49 (m, 1H), 2.99 (m, 2H), 3.46 (brs, 6H), 3.44 and 3.64 (2×d, 1H each, $J = 11$ Hz), 4.70 (d, 1H, $J = 9.5$ Hz), 4.87 (t, 1H, $J = 9.5$ Hz), 8.16 (s), 8.18 (s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 35.6 (t), 37.7 (d), 60.5 (d), 61.1 (t), 64.3 (t), 77.8 (s), 79.6 (d), 119.1 (s), 138.9 (d), 151.0 (s), 151.4 (d), 154.4 (s); FABMS, *m/z*: 324 ($M^+ + 1$). Anal. Calcd For $C_{14}H_{21}N_5O_4 \cdot 1.5H_2O$: C, 47.99; H, 6.90; N, 20.00. Found: C, 47.91; H, 6.93; N, 19.73.

21c: mp 190−191 °C dec; $[\alpha]^{25}_D$ +51.6° (*c* 0.45, MeOH); ^{1}H NMR (DMSO-d_6 + D_2O, 300 MHz) δ 1.69 (dd, 1H, $J = 6.5$, 13 Hz), 2.23 (dd, 1H, $J = 9$, 13 Hz), 2.51 (m, 1H overlapped with solvent peak), 3.06 (d, 2H, $J = 6$ Hz),3.47 and 3.62 (2×d, 1H each, $J = 11$ Hz), 4.11 (s, 3H), 4.75 (d, 1H, $J = 9.5$ Hz), 4.90 (t, 1H, $J = 9.5$ Hz), 4.98 (t, 1H, $J = 9.5$ Hz), 8.40 (s, 1H), 8.51 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 35.5 (t), 37.7 (d), 53.7 (d), 60.9 (q), 61.2 (t), 62.4 (t), 77.7 (s), 79.5 (d), 120.5 (s), 143.1 (d), 150.9 (d), 152.9 (s), 160.0 (s); FABMS, *m/z*: 311 ($M^+ + 1$). Anal. Calcd for $C_{13}H_{18}N_4O_5$: C, 50.31; H, 5.85; N, 18.06. Found: C, 50.24; H, 5.84; N, 17.93.

(1′*R*,2′*S*,3′*R*,4′*R*)-9-[1,4-Bis(hydroxymethyl)-1,2-dihydroxycyclopent-3-yl]-6-(dimethylamino)adenine (23a) and (1′*R*,2′*S*,3′*R*,4′*R*)-9-[1,4-Bis(hydroxymethyl)-1,2-dihydroxycyclopent-3-yl]-6-methoxyadenine (23c). Compound **22** (204 mg) was converted to **23a** (138 mg, 37%) and **23c** (14 mg, 4.0%) following the method just described above. **23a**: sticky nature; $[\alpha]^{25}_D$ −36.2° (*c* 0.29, MeOH). Anal. Calcd for $C_{14}H_{21}N_5O_4 \cdot H_2O$: C, 49.24; H, 6.79; N, 20.52. Found: C, 49.26; H, 6.75; N, 20.42. **23c**: mp 158−160 °C; $[\alpha]^{25}_D$ −51.0° (*c* 0.41, MeOH). Anal. Calcd for $C_{13}H_{18}N_4O_5 \cdot 2H_2O$: C, 49.77; H, 5.85; N, 17.86. Found: C, 49.75; H, 5.86; N, 17.48.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **9**, **11**, **15**, **16a**−**c**, **21a**, **21c**, and ^{1}H NMR spectra of **13** and **23a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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