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Carbocyclic nucleosides from enantiomeric, α-pinane-based aminodiols

Zsolt Szakonyi [a], Ferenc Fülöp [a,b,*]

[a] *Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*
[b] *Research Group of Stereochemistry of the Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*

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ABSTRACT

Starting from (1*R*,2*S*,3*S*,5*R*)- and (1*S*,2*R*,3*R*,5*S*)-6,6-dimethylspiro[bicyclo[3.1.1]heptane-2,2'-oxiran]-3-ol (−)-**8** and (+)-**8**, two comparative syntheses were developed for pinane-based chiral carbocyclic nucleosides. The regioselective ring opening of the spiro-oxirane ring of (−)-**8** and (+)-**8** with NaN_3 resulted in azidodiols (−)-**9** and (+)-**9**. Catalytic reduction of (−)-**9** and (+)-**9** furnished chiral aminodiols (−)-**10** and (+)-**10**, which were transformed by linear synthesis to purine-type nucleosides **16**–**18** through pyrimidine intermediates. Regioselective ring opening of the oxirane ring of (−)-**8** and (+)-**8** resulted in adenine-, cytosine- and uracil-based carbocyclic nucleosides **19**–**21** in a single-step synthesis.

1. Introduction

During the past decade, the discovery of carbocyclic nucleosides possessing potent antiviral and antitumour activity has led to an increasing demand for the production of new chiral, alicyclic nucleoside analogues.[1,2] Bioisosteric replacement of the oxygen in the sugar moiety with a methylene unit makes these compounds more resistant to hydrolysis without a loss of the biological activity. The first-generation carbocyclic compounds were similar to the adenosine analogue natural aristeomycin **1** and neplanocin A **2**, containing a cyclopentane or cyclopentene ring and two or three hydroxy groups on the ring, one of them typically as a hydroxymethyl substituent.[1,3–8] In recent years, conformationally locked, bicyclic and tricyclic analogues have also been successfully prepared.[1b,9–12] Some of these compounds possess noteworthy pharmacological activity, such as the antiviral North-methanocarbathymidine (N-MCT, **5**) or the species-independent A_3 receptor-selective agonist (*N*)-methanocarba-adenosine 5'-uronamides **6**.[12–18] The latter compounds clearly show that the primary hydroxy group is not essential for the biological activity (see Fig. 1).

The synthesis of carbanucleosides may follow different strategies: the convergent attachment of an intact heterocyclic base with an appropriately functionalized carbocyclic ring by substitution (e.g., through an activated hydroxy group) or by addition (ring opening of an epoxy function). Linear construction of the heterocycle from an amine substituent on the carbocycle is also possible, though often less successful strategy.[1,2]

As part of our systematic studies on 1,3-difunctional chiral monoterpenic building blocks,[19] we recently reported the synthesis of a (+)- and (−)-2-aminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol-type [(+)-**10** and (−)-**10**)] aminodiol library, starting from the readily available α-pinene enantiomers.[20] The resulting aminodiols were successfully applied as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes and in the regioselective ring closure of aminodiols towards chiral 1,3-heterocycles.[20,21]

Our present aim was the comparative synthesis of chiral aminodiol-based monoterpene nucleosides from pinane-based aminodiol enantiomers and their starting material epoxy alcohols following two strategies: linear synthesis of the base component on the 2-aminomethyl substituent of the pinane system and regioselective ring opening of the spiro-oxirane ring with various purine and pyrimidine bases.

2. Results and discussion

Aminodiols (+)-**10** and (−)-**10** were synthesized from commercially available (+)- and (−)-α-pinene by modification of literature methods.[20,22–24] Epoxidation of monoterpenes (+)-**7** and (−)-**7** with MCPBA, followed by allylic rearrangement and subsequent epoxidation resulted in the well-known stereohomogeneous epoxy alcohols (+)-**8** and (−)-**8**.[22–25] Synthesis of (+)-**10** and **(−)-10** was previously reported by the aminolysis of (+)-**8** and (−)-**8** with primary or secondary amines, followed by reductive debenzylation, with moderate overall yields.[20] In our present work, the reactions of (+)-**8** and (−)-**8** with NaN_3 in refluxing $EtOH/H_2O$ in the presence of a catalytic amount of NH_4Cl produced azidodiols (+)-**9** and (−)-**9** in a regioselective reaction (Scheme 1).[26,27] Catalytic reduction of (+)-**9** and (−)-**9** over Pd/C resulted in primary aminodiols (+)-**10** and (−)-**10** in excellent yield (78% overall yield from **8**).[†]

* Corresponding author. Tel.: +36 62 545564; fax: +36 62 545705.
E-mail address: fulop@pharm.u-szeged.hu (F. Fülöp).

[†] In the present experiments, apart from **11**–**13**, all of the reactions were carried out on both enantiomers, although only one of them is presented in the Schemes.

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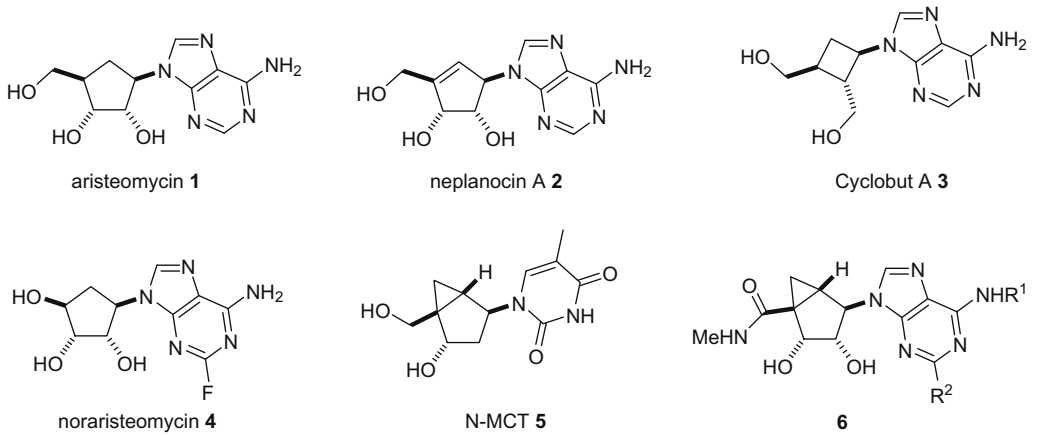
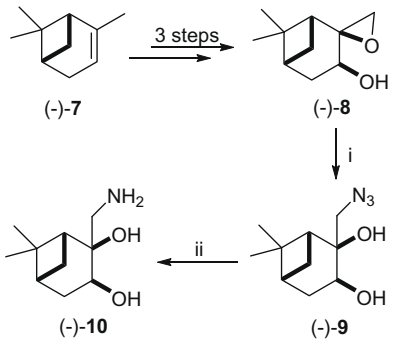


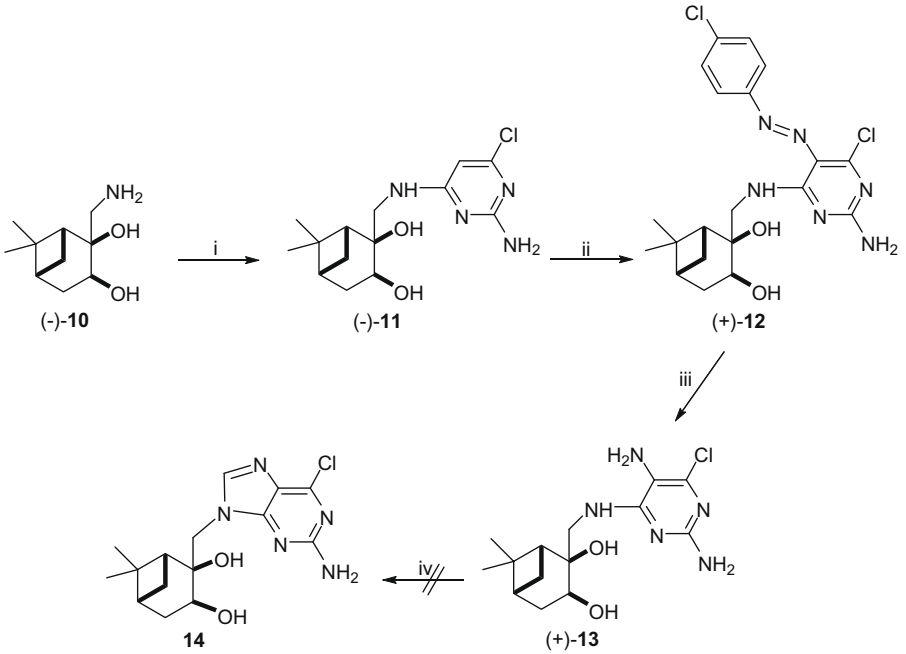
Figure 1. Pharmacologically active nucleoside analogues bearing an aminodiol moiety.



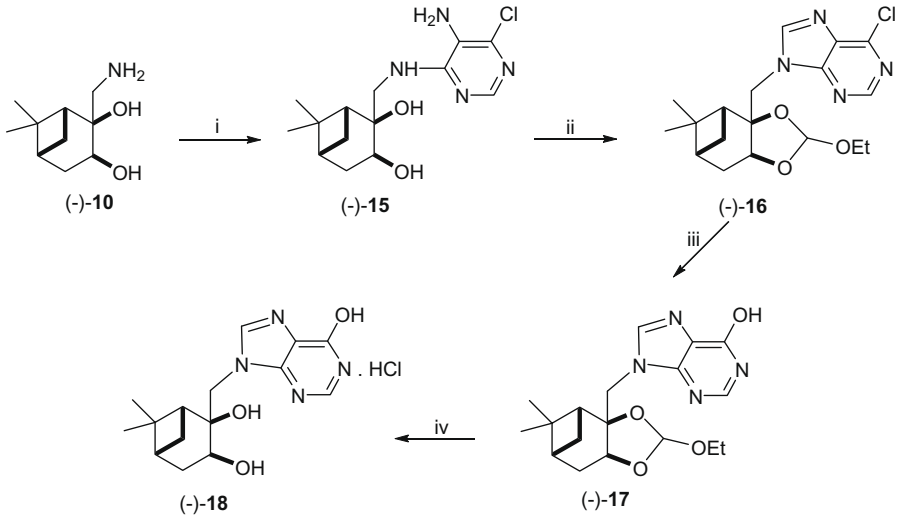
Scheme 1. Reagents and conditions: (i) 2.0 equiv NaN_3, 20% NH_4Cl, EtOH/H_2O, reflux, 36 h, 85%; (ii) 10% Pd/C, MeOH, 1 atm H_2, rt, 6 h, 92%.

In our first experiment, we attempted the linear synthesis of the base component from aminodiol (−)-**10** (Scheme 2).[17] Condensation of (−)-**10** with 2-amino-4,6-dichloropyrimidine resulted in (−)-**11**. Azaderivative (+)-**12** was then obtained by reaction between (−)-**11** and 4-chlorobenzenediazonium generated in situ. Reduction of (+)-**12** with Zn in acetic acid gave triaminopyrimidinyl derivative (+)-**13**. When (+)-**13** was treated with triethylorthoformate in hydrochloric acid, instead of the expected **14**, only a mixture of inseparable products was obtained, probably due to the inter- or intramolecular reactions of diol and aromatic amino groups and triethyl orthoformate.

We decided to repeat the above synthesis from 5-amino-4,6-dichloropyrimidine to reduce the possibility of side-reactions.[17] Condensation of (−)-**10** and (+)-**10** with 5-amino-4,6-dichloropyrimidine in refluxing *n*-BuOH containing Et_3N afforded (−)-**15** and (+)-**15**. Then, to form the imidazole ring of the purine analogues, (−)-**15** and (+)-**15** were treated with triethyl orthoformate in hydrochloric acid to give (−)-**16** and (+)-**16**. Besides imidazole ring formation, *cis* positioned hydroxy groups reacted with the excess of orthoformate to afford unique chiral orthoesters (−)-**16** and (+)-**16**. Compound (−)-**16** and (+)-**16** were converted into the hydroxy derivatives (−)-**17** and (+)-**17** by treatment with 0.25 M



Scheme 2. Reagents and conditions: (i) 2-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux, 24 h, 63%; (ii) 4-chloroaniline, HCl, H_2O, $NaNO_2$, NaOAc, HOAc, overnight, 91%; (iii) Zn powder, HOAc, H_2O/EtOH, reflux, 3 h, 73%; (iv) triethyl orthoformate, 12 M HCl, rt, overnight.



Scheme 3. Reagents and conditions: (i) 5-amino-4,6-dichloropyrimidine, Et_3N, *n*-BuOH, reflux, 24 h, 59%; (ii) triethyl orthoformate, 12 M HCl, rt, 36 h, 82%; (iii) 0.25 M NaOH, reflux, 6 h, 85%; (iv) 10% HCl, rt, 12 h, 67%.

NaOH at reflux for 6 h. Orthoesters (−)-**17** and (+)-**17** were then successfully hydrolysed to the final nucleoside analogues (−)-**18** and (+)-**18** by treatment with hydrochloric acid (Scheme 3).

An alternative synthesis of monoterpenic nucleoside analogues was carried out by a regioselective ring opening of the spiro-oxirane ring of (−)-**8** and (+)-**8** with various purine and pyrimidine bases, resulting in (−)-**19–21** and (+)-**19–21**.[28] Although the yields of the reactions were moderate, the desired nucleosides were obtained in a single-step reaction. The limitation of this method is that the yield dropped dramatically when bases with a strong electron-withdrawing substituent on the heterocyclic ring were applied, for example, the reaction failed when 5-fluorouracil was used (Scheme 4).

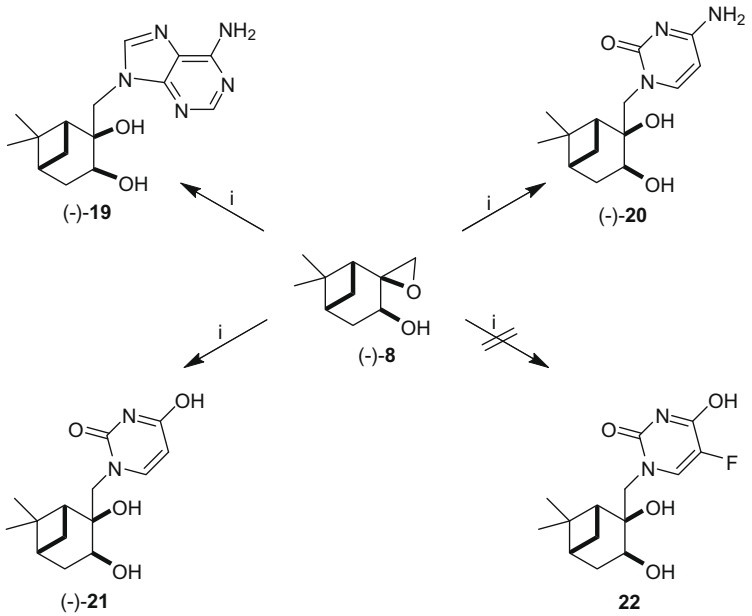
3. Conclusions

Pinane-based chiral epoxy alcohols (−)-**8** and (+)-**8** and aminodiols (−)-**10** and (+)-**10** are highly valuable building blocks for the synthesis of sterically constrained bicyclic nucleoside analogues. Both epoxy alcohols (−)-**8** and (+)-**8** and aminodiols (−)-**10** and (+)-**10** are readily available on a gram scale with high enantiopurity. Synthesis of the desired carbonucleosides has been successfully performed via two pathways. Aminodiols (−)-**10** and (+)-**10** were transformed by linear synthesis to purine-type nucleosides (−)-**16–18** and (+)-**16–18** through pyrimidine intermediates.

Regioselective ring opening of the oxirane ring of (−)-**8** and (+)-**8** resulted in adenine-, cytosine- and uracil-based carbocyclic nucleosides (−)-**19–21** and (+)-**19–21** in single-step syntheses. The reaction failed when 5-fluorouracil (a nucleoside base with a strong electron-withdrawing substituent on the heterocyclic ring) was applied.

4. Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at 400.13 MHz (^1H) and 100.61 MHz (^{13}C) [δ = 0



Scheme 4. Reagents and conditions: (i) 1.5 equiv base, 2.0 equiv dry K_2CO_3, dry DMF, 100 °C, 48 h, **19**: adenine (57%), **20**: cytosine (60%), **21**: uracil (49%), **22**: 5-fluorouracil.

(TMS)] in $CDCl_3$, D_2O or DMSO-d_6 in a 5-mm tube. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. J values are given in hertz. Microanalyses were performed on a Perkin–Elmer 2400 elemental analyser. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness).

The enantiomeric purities of the prepared epoxy alcohols and azidodiols were determined by means of GC measurements involving direct separation of the enantiomers on a CHIRASIL-DEX CB column (2500 × 0.25 mm I.D.) and were found to be >98%.

All the chemicals and solvents were used as supplied. (−)-(1*S*,5*S*)- and (+)-(1*R*,5*R*)-α-pinene are commercially available; epoxy alcohols (−)-**8** and (+)-**8** were prepared by a literature method, and were identical with those reported in the literature.[23,25]

4.1. (1*R*,2*S*,3*S*,5*R*)-2-(Azidomethyl)-6,6-dimethylbicyclo-[3.1.1]heptane-2,3-diol (−)-9

To a solution of epoxy alcohol **(−)-8** (1.92 g, 11.4 mmol) in EtOH (50 mL) and water (3.4 mL), NaN_3 (1.48 g, 22.8 mmol) and NH_4Cl (0.122 g, 2.3 mmol) were added. The reaction mixture was refluxed for 36 h, and the EtOH was then evaporated off. The resulting mixture was dissolved in water (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The combined organic layer was dried (Na_2SO_4) and evaporated, and the yellow oily crude product obtained was crystallized with *n*-hexane, resulting in a pale-yellow crystalline product.[29] Isolated compound: 2.05 g (85%); mp: 70–73 °C; $[\alpha]_D^{20} = -11.0$ (*c* 0.5, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.92 (3H, s), 1.28 (3H, s), 1.44 (1H, d, J = 10.4 Hz), 1.67 (1H, ddd, J = 2.4, 5.5, 14.1 Hz), 1.91–1.98 (1H, m), 2.10 (1H, t, J = 5.7 Hz), 2.20–2.31 (1H, m), 2.43–2.53 (1H, m), 2.57 (1H, s), 3.27 (1H, d, J = 12.3 Hz), 3.34 (1H, d, J = 12.3 Hz), 3.64 (1H, s), 4.09–4.17 (1H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.5, 28.0, 28.1, 37.5, 39.0, 40.9, 50.4, 61.4, 66.6, 76.0. Anal. Calcd for $C_{10}H_{17}N_3O_2$ (211.26): C, 56.85; H, 8.11; N, 19.89. Found: C, 56.98; H, 8.27; N, 19.63.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer (+)-**9** was synthesized analogously to (−)-**9**; $[\alpha]_D^{20} = +11.0$ (*c* 0.5, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*S*,3*S*,5*R*)-enantiomer. Anal. Calcd for $C_{10}H_{17}N_3O_2$ (211.26): C, 56.85; H, 8.11; N, 19.89. Found: C, 57.04; H, 8.19; N, 19.65.

4.2. (1*R*,2*S*,3*S*,5*R*)-2-Aminomethyl-6,6-dimethylbicyclo[3.1.1] heptane-2,3-diol (−)-10

To a suspension of palladium-on-carbon (5% Pd/C, 0.40 g) in MeOH (30 mL) was added azidodiol **(−)-9** (1.05 g, 5.0 mmol) in MeOH (15 mL), and the resulting mixture was stirred under a H_2 atmosphere (1 atm) at room temperature. When the reaction was complete, as indicated by TLC, the solution was filtered through a Celite pad and the solvent was removed, affording a colourless oily product **(−)-10**, which crystallized upon standing at ca. 4 °C. The crystalline product was recrystallized from *n*-hexane and was found to be identical with that reported in the literature.[20] Isolated compound: 0.85 g (92%); mp 61–63 °C; $[\alpha]_D^{20} = -7.5$ (*c* 0.25, EtOH, lit.:[20] −7.0, *c* = 0.25, EtOH); Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56. Found: C, 65.01; H, 10.49; N, 7.28.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer **(+)-10** was synthesized analogously to **(−)-10**, $[\alpha]_D^{20} = +7.0$ (*c* 0.25, EtOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*S*,3*S*,5*R*)-enantiomer. Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56. Found: C, 64.63; H, 10.51; N, 7.22.

4.3. (1*R*,2*S*,3*S*,5*R*)-2-[(2-Amino-6-chloropyrimidin-4-ylamino)methyl]-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (−)-11

A mixture of aminodiol (−)-**10** (0.370 g, 2.0 mmol) and 2-amino-4,6-dichloropyrimidine (0.420 g, 2.56 mmol) in dry Et_3N (2.3 mL and *n*-BuOH (11.0 mL) was refluxed under argon for 24 h. The solvent was then evaporated off under reduced pressure and the residue was purified by flash chromatography on a silica gel column (toluene/EtOH = 9/1), resulting in a white crystalline product. Isolated compound: 0.392 g (63%); mp: 159–162 °C; $[\alpha]_D^{20} = -22.0$ (*c* 0.1, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.05 (3H, s), 1.18 (3H, s), 1.37 (1H, d, J = 10.1 Hz), 1.55 (1H, ddd, J = 2.2, 5.1, 13.8 Hz), 1.78–1.84 (1H, m), 1.96 (1H, t, J = 5.7 Hz), 2.03–2.11 (1H, m), 2.29–2.39 (1H, m), 3.25 (1H, dd, J = 5.9, 13.4 Hz), 3.36 (1H, dd, J = 5.4, 13.4 Hz), 3.85 (1H, dt, J = 5.8, 9.0 Hz), 4.61 (1H, s), 5.16 (1H, d, J = 5.9 Hz), 5.88 (1H, s), 6.26 (2H, br s), 6.96 (1H, br s); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.7, 28.2, 28.5, 38.7, 39.1, 40.9, 49.7, 49.9, 65.7, 75.8, 93.3, 157.6, 163.5, 165.1. Anal. Calcd for $C_{14}H_{21}ClN_4O_2$ (312.80): C, 53.76; H, 6.77; N, 17.91. Found: C, 53.52; H, 6.97; N, 17.65.

4.4. (1*R*,2*S*,3*S*,5*R*)-2-[(2-Amino-6-chloro-5-(4-chlorophenyldiazenyl)pyrimidin-4-ylamino)methyl]-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (+)-12

4-Chloroaniline (0.123 g, 0.96 mmol) in 3 M HCl (0.77 mL) was treated at 0 °C with $NaNO_2$ (0.069 g, 0.99 mmol) in water (0.77 mL). The diazonium salt obtained was added to a mixture of (−)-**11** (0.260 g, 0.83 mmol), NaOAc (1.53 g), AcOH (3.84 mL) and water (3.84 mL), and was stirred overnight at room temperature. The resulting precipitate was filtered off and washed with cold water until neutral, to obtain yellow crystals. Isolated compound: 0.340 g (91%); mp: 249–253 °C; $[\alpha]_D^{20} = +24.0$ (*c* 0.1, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.00 (3H, s), 1.18 (3H, s), 1.40 (1H, d, J = 10.2 Hz), 1.54–1.63 (1H, m), 1.78–1.87 (1H, m), 1.89–1.95 (1H, m), 2.05–2.14 (1H, m), 2.31–2.42 (1H, m), 3.48 (1H, dd, J = 4.1, 13.4 Hz), 3.63 (1H, dd, J = 5.9, 13.4 Hz), 3.87–3.95 (1H, m), 4.68 (1H, s), 5.29 (1H, br d, J = 5.4 Hz), 7.57 (2H, d, J = 8.8 Hz), 7.75 (2H, d, J = 8.8 Hz), 10.58 (1H, br t, J = 4.7 Hz); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.7, 28.4, 28.6, 38.6, 39.1, 40.9, 50.2, 50.5, 66.1, 74.8, 119.8, 123.7, 130.3, 134.2, 151.6, 156.1, 161.9, 165.5. Anal. Calcd for $C_{20}H_{24}Cl_2N_6O_2$ (451.35): C, 53.22; H, 5.36; N, 18.62. Found: C, 53.43; H, 5.62; N, 18.31.

4.5. (1*R*,2*S*,3*S*,5*R*)-2-[(2,5-Diamino-6-chloropyrimidin-4-ylamino)methyl]-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (+)-13

A mixture of **(+)-12** (0.433 g, 0.96 mmol), Zn powder (0.530 g, 8.12 mmol), AcOH (0.2 mL), water (6.0 mL) and EtOH (6.0 mL) was refluxed under argon for 3 h. The reaction mixture was then filtered, the filtrate was evaporated down under reduced pressure and the crude reaction mixture was purified by p-TLC (EtOAc), resulting in (+)-**13** as a brown solid. Isolated compound: 0.230 g (73%); mp: 171–174 °C; $[\alpha]_D^{20} = +19.0$ (*c* 0.5, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.02 (3H, s), 1.19 (3H, s), 1.37 (1H, d, J = 9.8 Hz), 1.55 (1H, ddd, J = 2.3, 5.1, 13.7 Hz), 1.77–1.85 (1H, m), 1.94–1.99 (1H, m), 2.02–2.11 (1H, m), 2.30–2.39 (1H, m), 3.39 (2H, d, J = 5.6 Hz), 3.84–3.92 (1H, m), 4.84 (1H, br s), 4.96 (1H, br d, J = 6.3 Hz), 5.58 (2H, br s), 6.30 (1H, t, J = 5.5 Hz); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.1, 27.7, 28.0, 38.3, 38.6, 40.4, 49.3, 50.0, 65.2, 75.3, 113.2, 142.7, 156.1, 157.0. Anal. Calcd for $C_{14}H_{22}ClN_5O_2$ (327.81): C, 51.29; H, 6.76; N, 21.36. Found: C, 51.46; H, 6.99; N, 21.01.

4.6. (1*R*,2*S*,3*S*,5*R*)-2-[(5-Amino-6-chloropyrimidin-4-ylamino) methyl]-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (−)-15

A mixture of aminodiol (−)-**10** (0.370 g, 2.0 mmol) and 5-amino-4,6-dichloropyrimidine (0.420 g, 2.56 mmol) in dry Et_3N (2.3 mL) and *n*-BuOH (11.0 mL) was refluxed under argon for 24 h. The solvent was then evaporated off under reduced pressure and the residue was purified by flash chromatography on a silica gel column (toluene/EtOH = 9/1), resulting in a white crystalline product.

Isolated compound: 0.388 g (59%); mp: 203–205 °C; $[\alpha]_D^{20} = -15.0$ (*c* 0.1, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.05 (3H, s), 1.18 (3H, s), 1.37 (1H, d, *J* = 10.1 Hz), 1.51–1.60 (1H, m), 1.78–1.86 (1H, m), 1.93–1.99 (1H, m), 2.03–2.11 (1H, m), 2.31–2.39 (1H, m), 3.47 (1H, dd, *J* = 5.9, 13.4 Hz), 3.58 (1H, dd, *J* = 5.4, 13.4 Hz), 3.91 (1H, dt, *J* = 9.5, 11.2 Hz), 4.56 (1H, s), 5.09 (1H, br s), 5.16 (1H, d, *J* = 6.3 Hz), 6.58 (1H, t, *J* = 5.4 Hz), 7.70 (1H, s); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.6, 28.3, 28.5, 38.7, 39.1, 40.9, 49.7, 50.7, 65.6, 75.9, 137.5, 146.3, 153.1, 153.3. Anal. Calcd for $C_{14}H_{21}ClN_4O_2$ (312.80): C, 53.76; H, 6.77; N, 17.91. Found: C, 53.85; H, 6.98; N, 17.61.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer **(+)-15** was synthesized analogously to **(−)-15**; $[\alpha]_D^{20} = +14.5$ (*c* 0.1, MeOH); all the spectroscopic data and the mp were similar to those for the 1*R*,2*S*,3*S*,5*R* enantiomer. Anal. Calcd for $C_{14}H_{21}ClN_4O_2$ (312.80): C, 53.76; H, 6.77; N, 17.91. Found: C, 53.06; H, 6.94; N, 17.56.

4.7. (1*R*,2*S*,6*S*,8*R*)-2-[(6-Chloro-9*H*-purin-9-yl)methyl]-9,9-dimethyl-4-ethoxy-3,5-dioxatricyclo[6.1.1.0^{2,6}]decane (−)-16

A mixture of (−)-**15** (0.20 g, 0.64 mmol), triethyl orthoformate (3.7 mL) and 12 M HCl (0.19 mL) was stirred overnight under argon at room temperature. The reaction mixture was then concentrated under reduced pressure until dryness and the residue was purified by p-TLC (eluent EtOAc). Compound **16** was isolated as an oil. Isolated compound: 0.195 g (81%); oil; $[\alpha]_D^{20} = -124.0$ (*c* 0.155, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.19–1.24 (9H, m), 1.24 (3H, s), 1.25 (1H, d, *J* = 10.2 Hz), 1.68 (H, t, *J* = 5.9 Hz), 1.92–2.12 (4H, m), 2.32–2.41 (1H, m), 3.62 (2H, ddd, *J* = 2.7, 9.6, 16.6 Hz), 4.39 (1H, d, *J* = 7.6 Hz), 4.53 (1H, d, *J* = 14.2 Hz), 4.82 (1H, d, *J* = 14.2 Hz), 5.90 (1H, s), 8.39 (1H, s), 8.79 (1H, s); ^{13}C NMR (DMSO-d_6) δ (ppm): 15.5, 23.8, 25.2, 26.8, 33.3, 40.2, 45.9, 51.4, 52.5, 61.7, 73.1, 86.6, 116.1, 131.4, 147.5, 148.3, 152.1, 153.1. Anal. Calcd for $C_{18}H_{23}ClN_4O_3$ (378.85): C, 57.07; H, 6.12; N, 14.79. Found: C, 57.40; H, 6.35; N, 14.51.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer (+)-**16** was synthesized analogously to (−)-**16**; $[\alpha]_D^{20} = +119.0$ (*c* 0.155, MeOH); all the spectroscopic data and the mp were similar to those for the 1*R*,2*S*,3*S*,5*R* enantiomer. Anal. Calcd for $C_{18}H_{23}ClN_4O_3$ (378.85): C, 57.07; H, 6.12; N, 14.79. Found: C, 57.39; H, 6.28; N, 14.68.

4.8. (1*R*,2*S*,6*S*,8*R*)-2-[(6-Hydroxy-9*H*-purin-9-yl)methyl]-9,9-dimethyl-4-ethoxy-3,5-dioxatricyclo[6.1.1.0^{2,6}]decane (−)-17

A mixture of (−)-**16** (0.15 g, 0.164 mmol) and 0.25 M NaOH (5.1 mL) was refluxed for 5 h, whereafter the reaction mixture was cooled and the solvent was removed under reduced pressure until dryness, and the residue was purified by p-TLC (eluent EtOAc) to afford **(−)-17** as white crystals. Isolated compound: 0.121 g (85%); mp: 280–284 °C; $[\alpha]_D^{20} = -18.0$ (*c* 0.1, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.19 (6H, s overlapped with t), 1.24 (3H, s), 1.25 (1H, d, *J* = 10.2 Hz), 1.69 (H, t, *J* = 5.4 Hz), 1.83–1.95 (3H, m), 2.03–2.13 (1H, m), 2.29–2.38 (1H, m), 3.58 (2H, ddd, *J* = 2.1, 7.1, 14.2 Hz), 4.41 (1H, d, *J* = 14.4 Hz), 4.53 (1H, d, *J* = 7.7 Hz), 4.61 (1H, d, *J* = 14.4 Hz), 6.00 (1H, s), 7.88 (1H, s), 8.09 (1H, d, *J* = 3.8 Hz), 12.29 (1H, br s); ^{13}C NMR (DMSO-d_6) δ (ppm): 15.8, 23.9, 25.2, 27.2, 33.4, 38.6, 40.9, 46.1, 51.0, 61.2, 72.7, 86.5, 115.7, 123.5, 141.8, 145.8, 149.4, 157.0. Anal. Calcd for $C_{18}H_{24}N_4O_4$ (360.41): C, 59.99; H, 6.71; N, 15.55. Found: C, 60.20; H, 6.86; N, 15.31.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer (+)-**17** was synthesized analogously to (−)-**17**; $[\alpha]_D^{20} = +17.0$ (*c* 0.1 MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*S*,3*S*,5*R*)-enantiomer. Anal. Calcd for $C_{18}H_{24}N_4O_4$ (360.41): C, 59.99; H, 6.71; N, 15.55. Found: C, 60.17; H, 6.89; N, 15.39.

4.9. (1*R*,2*S*,3*S*,5*R*)-2-[(6-Hydroxy-9*H*-purin-9-yl)methyl]-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol hydrochloride (−)-18

A mixture of (−)-**17** (0.215 g, 0.60 mmol) and 3 M HCl (10.0 mL) was stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure until dryness, resulting in (−)-**18** as white crystals in >98% purity (based on NMR measurement). Isolated compound: 0.136 g (67%); mp: 304–307 °C; $[\alpha]_D^{20} = -19.0$ (*c* 0.1, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.18 (3H, s), 1.19 (3H, s), 1.33 (1H, d, *J* = 9.8 Hz), 1.57 (1H, dd, *J* = 5.4, 2.3 Hz), 1.64 (H, t, *J* = 5.8 Hz), 1.81–1.87 (1H, m), 2.00–2.08 (1H, m), 2.32–2.42 (1H, m), 4.07 (1H, dd, *J* = 5.6, 9.7 Hz), 4.20 (2H, dd, *J* = 14.0, 23.6 Hz), 8.20 (1H, s), 8.62 (1H, s), 12.72 (1H, br s); ^{13}C NMR (DMSO-d_6) δ (ppm): 24.4, 28.3, 28.4, 38.6, 39.1, 40.9, 49.3, 52.9, 65.0, 74.9, 119.5, 141.5, 147.9, 148.7, 155.4. Anal. Calcd for $C_{15}H_{21}ClN_4O_3$ (340.81): C, 59.20; H, 6.62; N, 18.41. Found: C, 59.36; H, 6.88; N, 18.20.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer (+)-**18** was synthesized analogously to (−)-**18**; $[\alpha]_D^{20} = +17.0$ (*c* 0.1 MeOH); all the spectroscopic data and the mp were similar to those for the 1*R*,2*S*,3*S*,5*R* enantiomer. Anal. Calcd for $C_{15}H_{21}ClN_4O_3$ (340.81): C, 59.20; H, 6.62; N, 18.41. Found: C, 59.51; H, 6.93; N, 18.26.

4.10. General procedure for the ring opening of epoxy alcohols (−)-8 and (+)-8 with nucleoside bases

A mixture of the corresponding base (1.4 mmol, (−)-**19** and (+)-**19**: adenine, (−)-**20** and (+)-**20**: cytosine, (−)-**21** and (+)-**21**: uracil), K_2CO_3 (0.260 g, 1.89 mmol), and 18-crown-6 (0.150 g, 0.55 mmol) was suspended in anhydrous DMF (5.0 mL). A solution of (−)-**8** or (+)-**8** (0.160 g, 0.94 mmol) in anhydrous DMF was added to the mixture under argon at room temperature. After stirring for 0.5 h, the mixture was heated at 100 °C for 48 h. After filtration and evaporation, the crude product was purified by flash chromatography on a silica gel column ($CHCl_3$/MeOH = 9/1), which resulted in a white crystalline product.

4.10.1. (1*R*,2*S*,3*S*,5*R*)-2-[(6-Amino-9*H*-purin-9-yl)methyl]-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (−)-19

Isolated compound: 0.165 g (57%); mp: 236–239 °C; $[\alpha]_D^{20} = -19.0$ (*c* 0.125, MeOH ee 98%); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.15 (3H, s), 1.22 (3H, s), 1.30 (1H, d, *J* = 9.9 Hz), 1.50–1.61 (2H, m), 1.77–1.86 (1H, m), 1.95–2.05 (1H, m), 2.31–2.43 (1H, m), 4.05 (1H, dt, *J* = 5.9, 11.8 Hz), 4.12 (1H, dd, *J* = 14.4, 16.1 Hz), 4.62 (1H, s), 5.29 (1H, d, *J* = 6.4 Hz), 7.14 (2H, s), 8.05 (1H, s), 8.13 (1H, s); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.7, 27.4, 27.5, 37.8, 38.3, 40.0, 48.3, 51.1, 64.3, 74.3, 118.0, 142.2, 150.4, 152.2, 155.8. Anal. Calcd for $C_{15}H_{21}N_5O_2$ (303.36): C, 59.39; H, 6.98; N, 23.09. Found: C, 59.61; H, 7.23; N, 22.87.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer (+)-**19** was synthesized analogously to (−)-**19**; $[\alpha]_D^{20} = +21.0$ (*c* 0.1, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*S*,3*S*,5*R*)-enantiomer. Anal. Calcd for $C_{15}H_{21}N_5O_2$ (303.36): C, 59.39; H, 6.98; N, 23.09. Found: C, 59.53; H, 7.17; N, 22.78.

4.10.2. 4-Amino-1-[((1*R*,2*S*,3*S*,5*R*)-2,3-dihydroxy-6,6-dimethylbicyclo[3.1.1]heptan-2-yl)methyl]pyrimidin-2(1*H*)-one (−)-20

Isolated compound: 0.160 g (60%); mp: 259–260 °C; $[\alpha]_D^{20} = -17.0$ (*c* 0.125, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.07 (3H, s), 1.18 (3H, s), 1.31 (1H, d, *J* = 9.9 Hz), 1.51 (1H, ddd, *J* = 2.2, 5.5, 13.8 Hz), 1.75–1.85 (2H, m), 1.98–2.07 (1H, m), 2.27–2.38 (1H, m), 3.70 (2H, dd, *J* = 14.1, 15.5 Hz), 4.00 (1H, dt, *J* = 5.7, 9.5 Hz), 4.64 (1H, s), 5.11 (1H, d, *J* = 6.6 Hz), 5.59 (1H, d, *J* = 7.1 Hz), 6.91 (2H, br d, *J* = 24.7 Hz), 7.52 (1H, d, *J* = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.2, 27.4, 27.5, 37.8, 38.3, 40.0, 48.8, 55.5, 64.0, 75.3, 92.3, 147.8, 157.0, 165.7. Anal. Calcd for $C_{14}H_{21}N_3O_3$ (279.33): C, 60.20; H, 7.58; N, 15.04. Found: C, 60.33; H, 7.87; N, 15.86.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer (+)-**20** was synthesized analogously to (−)-**20**; $[\alpha]_D^{20} = +20.0$ (*c* 0.1, MeOH); all the spectroscopic data and the mp were similar to those for the 1*R*,2*S*,3*S*,5*R* enantiomer. Anal. Calcd for $C_{14}H_{21}N_3O_3$ (279.33): C, 60.20; H, 7.58; N, 15.04. Found: C, 60.42; H, 7.77; N, 14.79.

4.10.3. 1-[((1*R*,2*S*,3*S*,5*R*)-2,3-Dihydroxy-6,6-dimethylbicyclo[3.1.1]-heptan-2-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-dione (−)-21

Isolated compound: 0.131 g (49%); mp: 235–237 °C; $[\alpha]_D^{20} = -28.0$ (*c* 0.125, MeOH ee >98%); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.05 (3H, s), 1.19 (3H, s), 1.32 (1H, d, *J* = 10.1 Hz), 1.51 (1H, dd, *J* = 5.0, 13.3 Hz), 1.76–1.85 (2H, m), 2.02–2.11 (1H, m), 2.29–2.40 (1H, m), 3.62 (1H, d, *J* = 13.8 Hz), 3.73 (1H, d, *J* = 13.8 Hz), 3.98 (1H, dt, *J* = 5.7, 9.9 Hz), 4.43 (1H, s), 5.35 (1H, d, *J* = 6.4 Hz), 5.46 (1H, dd, *J* = 2.1, 7.8 Hz), 7.58 (1H, d, *J* = 7.8 Hz), 11.12 (1H, s); ^{13}C NMR (DMSO-d_6) δ (ppm): 23.2, 27.4, 27.5, 37.7, 38.2, 39.9, 48.7, 54.2, 64.0, 75.0, 99.6, 147.6, 151.8, 163.7. Anal. Calcd for $C_{14}H_{20}N_1O_4$ (280.32): C, 59.99; H, 7.19; N, 9.99. Found: C, 60.28; H, 7.51; N, 9.82.

The (1*S*,2*R*,3*R*,5*S*)-enantiomer (+)-**21** was synthesized analogously to (−)-**21**; $[\alpha]_D^{20} = +22.0$ (*c* 0.1, MeOH); all the spectroscopic data and the mp were similar to those for the (1*R*,2*S*,3*S*,5*R*)-enantiomer. Anal. Calcd for $C_{14}H_{20}N_1O_4$ (280.32): C, 59.99; H, 7.19; N, 9.99. Found: C, 60.36; H, 7.41; N, 9.73.

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