Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 5050–5055
Tetrahedron

Chemoenzymatic synthesis of novel adenosine carbanucleoside analogues containing a locked 3′-methyl-2′,3′-β-oxirane-fused system

Yoann Aubin,[a] Gérard Audran,[a,*] Nicolas Vanthuyne[b] and Honoré Monti[a]

[a]*Laboratoire de Réactivité Organique Sélective, U.M.R. 6180 'Chirotechnologies: catalyse et biocatalyse', Université Paul Cézanne—Aix-Marseille III, 13397 Marseille Cedex 20, France*
[b]*Laboratoire de Stéréochimie Dynamique et Chiralité, U.M.R. 6180 'Chirotechnologies: catalyse et biocatalyse', Université Paul Cézanne—Aix-Marseille III, 13397 Marseille Cedex 20, France*

Received 14 December 2006; revised 19 March 2007; accepted 20 March 2007
Available online 24 March 2007

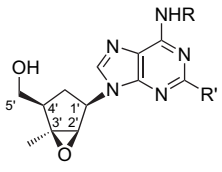
Abstract—Starting from a readily available enantiopure building block, a straightforward enantioselective approach to 3′-methyl-2′,3′-β-oxirane-fused carbanucleosides bearing adenosine analogues is detailed. The key steps in the syntheses involved a lipase-catalyzed regioselective monoacylation of a diol to obtain the key intermediate and direct coupling of this key intermediate with diversely substituted purine nucleobases under Mitsunobu reaction conditions providing only the N^9 target molecules.

1. Introduction

Carbocyclic nucleosides (carbanucleosides) are nucleoside analogues in which a methylene group has replaced the oxygen atom of the furanose ring.[1] These analogues display similar biological activities to their parent nucleosides with the advantage that they are unaffected by phosphorylases or hydrolases that cleave the glycosidic bond of natural nucleosides.[2] Independently of the structure of the nucleobase, and its possible further substitutions, the most relevant modifications that enhance biological properties of carbanucleosides are related to the nature and number of substituents on the carbapentofuranose glycon[3] and oxirane-fused,[4] or cyclopropane-fused,[3k,5] modifications of this glycon. Indeed, the fused three-membered ring of these bicyclic nucleoside analogues has a profound impact on fixing the conformation and the puckering of the cyclopentane ring.[6] In a first approach in the racemic series, we recently reported on the stereoselective synthesis of novel conformationally locked carbanucleosides in view of their potential biological relevance.[7]

Nevertheless, availability of both enantiomers of a carbocyclic nucleoside is very important because different pharmacological as well as toxicological properties of the opposite enantiomers have been observed[8] and, remarkably, it has been shown also that the two enantiomers of the same chiral compound can display similar biological activity.[9] This highlights the use of lipase-catalyzed kinetic resolution of racemic compounds, each enantiomer having its own potential utility.

As a logical continuation of our interest in the synthesis of 3′-methyl-branched carbapentofuranose derivatives,[10] and bearing in mind the potential usefulness of carbocyclic nucleosides built onto a rigid pseudosugar template, we wish to report herein in full the chemoenzymatic synthesis of novel 2′,3′-β-oxirane-fused carbanucleosides (Fig. 1). One attractive improvement in this approach is that we can build a rather complex molecular scaffold with controlled diastereoselectivity using very simple reagents and without the drudgery of protective/deprotective sequences.



1a R = ◁ R' = H
1b R = H R' = H
1c R = ◁ R' = NH_2

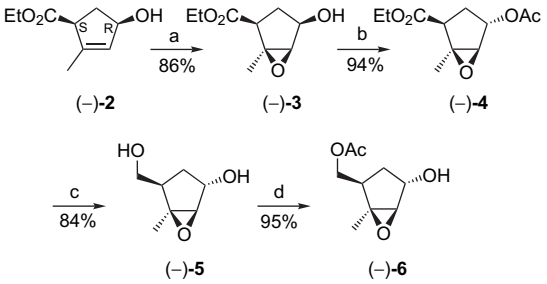
Figure 1.

Keywords: Carbocyclic nucleosides; Mitsunobu coupling reaction; Stereocontrolled epoxidation; Lipase regioselectivity.
* Corresponding author. Tel.: +33 (0)491288882; e-mail: g.audran@univ-cezanne.fr

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.122

2. Results and discussion

We recently reported the straightforward synthesis of the required enantiopure building block, ethyl (1*S*,4*R*)-4-hydroxy-2-methylcyclopent-2-ene-1-carboxylate, (−)-**2**, and its enantiomer through enzymatic kinetic resolution of the corresponding racemic **2** (Scheme 1).[11]



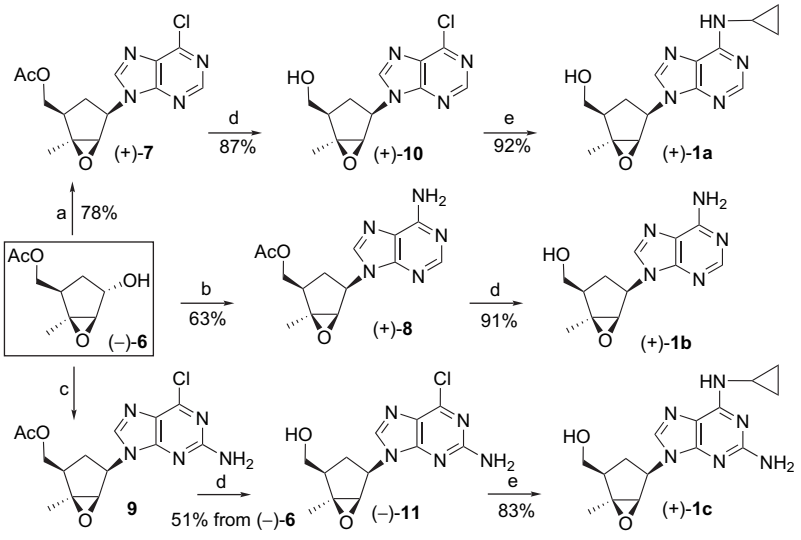
Scheme 1. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2; (b) Ph_3P, DIAD, AcOH, THF; (c) $LiAlH_4$, ether; (d) RML (*Rhysomucor meihei* lipase), vinyl acetate.

According to Hembest's rule,[12] this compound underwent hydroxyl-directed epoxidation by treatment with *m*-chloroperbenzoic acid at 0 °C in CH_2Cl_2 to produce the expected β-epoxide (−)-**3** in 86% yield. The inversion of the alcohol configuration of (−)-**3** was efficiently accomplished using a Mitsunobu reaction.[13] Compound (−)-**3** was treated with acetic acid in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine to afford the corresponding inverted acetate (−)-**4** in 94% yield after purification in a silica gel column. This accomplished, carboethoxy acetate (−)-**4** was readily reduced to the corresponding diol (−)-**5** in 84% yield by exposure to lithium aluminum hydride at 0 °C. At this stage, attempts to acylate unequivocally the primary hydroxyl group under common and convenient Ac_2O/Pyr or CH_3COCl/CH_2Cl_2/collidine conditions[14] failed, and the concomitant formation of the secondary acetate competed even at low temperature. This regioselective problem was solved by lipase-catalyzed monoacylation. Exposure of (−)-**5** to *Rhysomucor meihei* lipase (RML, lipozyme RMIM, Novo Nordisk A/S) and vinyl acetate at room temperature for 1 h provided the expected primary acetate (−)-**6** as the sole product in 95% yield.

With the desired compound (−)-**6** in hand, the synthesis of the target carbanucleosides **1a–c** is depicted in Scheme 2 using a Mitsunobu coupling as the key step. Thus, reaction of (−)-**6** chloropurine, adenine, and 2-amino-6-chloropurine, gave the alkylated derivatives (+)-**7** (78% yield), (+)-**8** (63% yield), and **9** (contaminated with triphenylphosphine oxide), respectively.

In each case, the desired N^9-alkylated compound was the only compound isolated with no traces of the alternative N^7-alkylated product observed (see infra). Cleavage of the acetyl protecting group in (+)-**8** with methanolic ammonia afforded the target molecule (+)-**1b** in 91% yield. The target molecules (+)-**1a** and (+)-**1c** were obtained using a two-step procedure: (i) deacetylation of derivatives (+)-**7** and **9** with methanolic ammonia to give (+)-**10** (87% yield) and (−)-**11** (51% yield, two steps from (−)-**6**) and (−)-**11** conversion of the 6-chloro group into 6-aminocyclopropyl group using cyclopropylamine in THF to obtain (+)-**1a** (92% yield) and (+)-**1c** (83% yield), respectively.

While the most direct way to accomplish structural elucidation of **1a–c** would be to obtain a crystal structure, unfortunately these derivatives proved to be difficult to crystallize, as they were fine powders. Typically, the structure of compound (+)-**1b** was secured using 2D-NMR spectroscopy. NOESY experiments were employed to determine the stereochemical configuration, and HMBC sequences confirmed the N^9-isomer (Fig. 2). Significant NOE effects were found between H-1′ (δ 4.99) and CH_3-3′ (δ 1.48), H-8 (δ 8.11) and H_β-6′ (δ 1.29), H-8 and H-5′ (δ 3.67). Long-range proton–carbon correlations were found between H-1′ (δ 4.99) and C-4 (δ 149.7), H-2 (δ 8.15) and C-4 (δ 149.7), H-2 and C-6 (δ 156.2). Likewise, the high optical purity of (+)-**1b** was verified by chiral HPLC (Fig. 3).



Scheme 2. Reagents and conditions: (a) Ph_3P, DIAD, 6-chloropurine, THF; (b) Ph_3P, DIAD, adenine, THF; (c) Ph_3P, DIAD, 2-amino-6-chloropurine, THF; (d) ammonia (7 N in methanol); (e) cyclopropylamine–THF (1:5), 12 h, 50 °C.

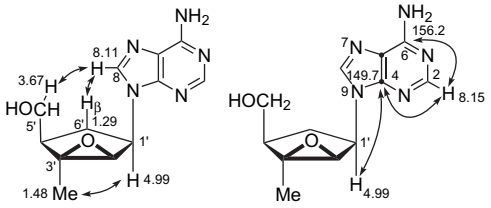


Figure 2. Selected NOE and HMBC correlations for (+)-**1b**.

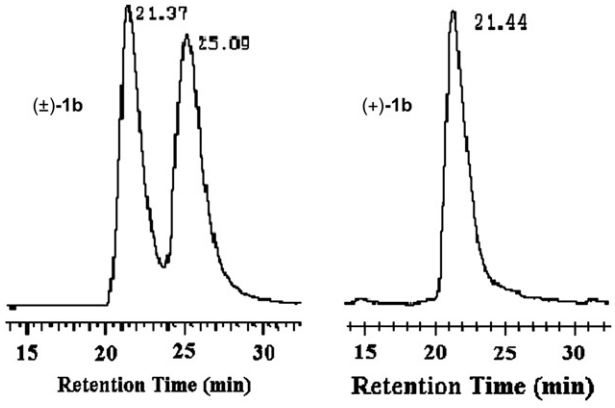


Figure 3. Chiral HPLC diagrams of (±)-**1b** and (+)-**1b** (conditions of analyses in Section 4).

3. Conclusion

In conclusion, we have developed an efficient route for the synthesis of conformationally locked 3′-methyl-2′,3′-β-oxirane-fused carbocyclic nucleosides bearing diversely substituted adenosine analogues in enantiomerically pure form. Key reactions developed under this program include lipase-promoted regioselective monoacylation of a diol and direct Mitsunobu coupling of the suitable alcohol precursor bearing the desired 3′-methyl-2′,3′-β-oxirane-fused scaffold with purine nucleobases. Since both the starting building blocks (−)-**2** and (+)-**2** are available through enzymatic kinetic resolution of the corresponding racemic **2**, either enantiomer of the target molecules is accessible.

4. Experimental

4.1. General chemical procedures

All air and/or water sensitive reactions were carried out under an argon atmosphere with dry, freshly distilled solvents using standard syringe–cannula/septa techniques. All corresponding glasswares were oven-dried (80 °C) and/or carefully dried in line with a flameless heat gun. All solvents were distilled under an argon atmosphere: THF from a blue solution of sodium-benzophenone ketyl radical prior to use and CH_2Cl_2, benzene, toluene, and DMF from CaH_2. Routine monitoring of reactions was done using Merck Silica gel 60 F_{254}, aluminum supported TLC plates; spots were visualized using a UV light and ethanolic acidic *p*-anisaldehyde solution or ethanolic phosphomolybdic solution, followed by heating. Purification by means of column chromatography was performed with Silica gel 60 (230–400 mesh) and gradients of Et_2O/petroleum ether as eluent, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, C_6D_6 or DMSO-d_6 solutions on a Bruker AM-300 or Bruker AM-200 spectrometers (Bruker AM-500 spectrophotometer for NOESY and HMBC experiments). Chemical shifts (δ) in parts per million are reported using residual non-deuterated solvents as internal reference. The analytical chiral HPLC experiments were performed on a unit composed of a Merck D-7000 system manager, Merck-Lachrom L-7100 pump, Merck-Lachrom L-7360 oven, and on-line Jasco CD-1595 circular dichroism detector. The column used is Chiralcel OD-H (250×4.6 mm; 5 μm) from Chiral Technologies Europe (Illkirch, France) with hexane/*i*-PrOH (90/10) and a flow rate of 1 mL/min. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Microanalyses were performed at our University. Melting points are uncorrected. Infrared spectra were obtained as films or KBr pellets using a Perkin–Elmer 1600 FTIR spectrophotometer.

4.1.1. (1*S*,2*S*,4*S*,5*R*)-4-Hydroxy-1-methyl-6-oxa-bicyclo[3.1.0]hexane-2-carboxylic acid ethyl ester (−)-3. To a stirred solution of (−)-**2** (3.00 g, 17.6 mmol) in CH_2Cl_2 (30 mL) was added *m*-CPBA (5.20 g, 22.9 mmol, 77 wt % in water) at 0 °C. The solution was allowed to warm to rt. After stirring for 2 h, the mixture was poured into a solution of Na_2SO_3 (5.80 g, 45.8 mmol) and was extracted with CH_2Cl_2. The organic extracts were combined, washed with a saturated solution of $NaHCO_3$, dried, filtered, and concentrated to afford after purification by column chromatography 2.82 g (86%) of (−)-**3**. Mp 87 °C. $[\alpha]_D^{25}$ −13.6 (*c* 1.0, $CHCl_3$). IR (KBr): ν 3451, 1735, 1247, 1127 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 4.32–4.19 (m, 1H), 4.17 (q, *J*=7.2 Hz, 2H), 3.27 (d, *J*=1.3 Hz, 1H), 2.70 (dd, *J*=10.2, 8.2 Hz, 1H), 2.17 (dt, *J*=13.2, 8.0 Hz, 1H), 1.65 (ddd, *J*=13.2, 10.2, 8.3 Hz, 1H), 1.52 (s, 3H), 1.26 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.2 (C), 71.4 (CH), 64.8 (CH), 63.2 (C), 60.8 (CH_2), 46.6 (CH), 32.0 (CH_2), 16.9 (CH_3), 14.2 (CH_3). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.80; H, 7.68.

4.1.2. (1*S*,2*S*,4*S*,5*R*)-4-Acetoxy-1-methyl-6-oxa-bicyclo[3.1.0]hexane-2-carboxylic acid ethyl ester (−)-4. A stirred solution of (−)-**3** (2.00 g, 10.7 mmol, 1 equiv), acetic acid (0.80 mL, 14.0 mmol, 1.3 equiv), and PPh_3 (3.70 g, 14.0 mmol, 1.3 equiv) in THF (20 mL) was immersed in an ice bath and DIAD (2.80 mL, 14.0 mmol, 1.3 equiv) was slowly added to maintain the temperature below 10 °C. Upon completion of the addition, the mixture was allowed to warm to rt and stirred for 1 h. The solvent was removed in vacuo and the residue was directly chromatographed (gradients of petroleum ether/diethyl ether as eluent) to afford (−)-**4** (2.30 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ −70.4 (*c* 1, $CHCl_3$). IR (neat): ν 1763, 1751, 1241, 1131 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.07 (d, *J*=5.7 Hz, 1H), 4.07 (m, 2H), 3.16 (s, 1H), 2.87 (dd, *J*=9.9, 8.4 Hz, 1H), 1.99 (ddd, *J*=15.2, 10.3, 5.9 Hz, 1H), 1.93 (s, 3H), 1.80 (dd, *J*=14.7, 8.5 Hz, 1H), 1.47 (s, 3H), 1.16 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (C), 169.8 (C), 72.9 (CH), 64.0 (C), 61.8 (CH), 60.5 (CH_2), 45.9 (CH), 31.5 (CH_2), 20.7 (CH_3), 16.0 (CH_3), 13.9 (CH_3). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found: C, 57.71; H, 7.04.

4.1.3. (1*R*,2*S*,4*R*,5*S*)-4-(Hydroxymethyl)-5-methyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (−)-5. A solution of (−)-**4**

(2.00 g, 8.70 mmol, 1 equiv) in dry diethyl ether (30 mL) was slowly added at 0 °C to a stirred slurry of $LiAlH_4$ (660 mg, 17.4 mmol, 2 equiv) in dry diethyl ether (50 mL). After 1 h at 0 °C, Celite (18 g) and $Na_2SO_4 \cdot 10H_2O$ (18 g) were added and the solution was allowed to warm to rt and stirred for a further 1 h. The reaction mixture was filtered through a pad of $MgSO_4$ and concentrated. Purification of the residue by column chromatography (gradients petroleum ether/diethyl ether as eluent) afforded 1.06 g (84%) of pure (−)-**5** as a colorless oil. $[\alpha]_D^{25}$ −38.8 (*c* 1, $CHCl_3$). IR (neat): ν 3419, 1132, 1035 cm^{-1}. ^1H NMR (300 MHz, C_6D_6): δ 4.25 (d, *J*=5.5 Hz, 1H), 3.78 and 3.72 (ABX, *J*=10.7, 5.8, 5.6 Hz, 2H), 3.20 (s, 1H), 2.32 (ddt, *J*=9.8, 8.1, 5.7 Hz, 1H), 1.69 (dd, *J*=14.1, 8.0 Hz, 1H), 1.55 (ddd, *J*=14.1, 9.7, 5.4 Hz, 1H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 70.9 (CH), 65.5 (C), 65.3 (CH), 62.3 (CH_2), 42.2 (CH), 34.6 (CH_2), 16.3 (CH_3). Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.61; H, 8.41.

4.1.4. Acetic acid (1*S*,2*R*,4*S*,5*R*)-4-hydroxy-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-ylmethyl ester (−)-6. A mixture of (−)-**5** (1.00 g, 6.90 mmol) and RML (100 mg) in 40 mL of vinyl acetate was magnetically stirred at rt for 1 h while monitoring the progress of the reaction by TLC. After completion of the reaction, the mixture was filtered, the solvent was removed in vacuo, and the residue was directly chromatographed (gradients petroleum ether/diethyl ether as eluent) to give 1.22 g (95%) of pure (−)-**6** as a colorless oil. $[\alpha]_D^{25}$ −49.6 (*c* 1, $CHCl_3$). IR (neat): ν 3329, 1756, 1142 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.28 (d, *J*=5.3 Hz, 1H), 4.14 and 4.11 (ABX, *J*=11.1, 7.6, 6.4 Hz, 2H), 3.20 (s, 1H), 2.41 (dq, *J*=9.4, 7.3 Hz, 1H), 2.08 (br s, OH), 2.04 (s, 3H), 1.70 (dd, *J*=14.0, 7.9 Hz, 1H), 1.49 (s, 3H), 1.41 (ddd, *J*=14.0, 9.9, 5.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1 (C), 70.9 (CH), 65.6 (CH), 64.6 (C), 64.3 (CH_2), 39.6 (CH), 35.1 (CH_2), 20.9 (CH_3), 16.5 (CH_3). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.21; H, 7.62.

4.1.5. Acetic acid (1*S*,2*R*,4*R*,5*R*)-4-(6-chloro-9*H*-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-ylmethyl ester (+)-7. Diisopropyl azodicarboxylate (0.72 mL, 3.6 mmol, 1.5 equiv) was added dropwise to a solution of PPh_3 (950 mg, 3.6 mmol, 1.5 equiv) in freshly distilled THF (50 mL) kept under an argon atmosphere at 0 °C. The mixture was stirred for 30 min and then 6-chloropurine was added (556 mg, 3.6 mmol, 1.5 equiv). The mixture was stirred for an additional 30 min and then a solution of epoxide (−)-**6** (450 mg, 2.4 mmol, 1 equiv) in dry THF (5 mL) was added slowly. The cooling bath was removed and the mixture was stirred at rt for 12 h. The volatiles were evaporated in vacuo and the resulting residue was purified by column chromatography using a gradient of petroleum ether/ethyl acetate as the eluent to give the protected 6-chloropurine carbanucleoside (+)-**7** (252 mg, 78%) as a white solid. Mp 103 °C. $[\alpha]_D^{25}$ +6.8 (*c* 1, $CHCl_3$). IR (KBr): ν 1742, 1238, 1136 cm^{-1}. ^1H NMR (75 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.42 (s, 1H), 5.19 (dd, *J*=9.2, 8.1 Hz, 1H), 4.30 and 4.23 (ABX, *J*=11.1, 6.5, 6.4 Hz, 2H), 3.61 (d, *J*=0.7 Hz, 1H), 2.56–2.48 (m, 1H), 2.44 (dt, *J*=12.2, 7.7 Hz, 1H), 2.06 (s, 3H), 1.58 (s, 3H), 1.45 (dt, *J*=12.5, 9.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.71 (C), 151.9 (CH), 151.7 (C), 151.1 (C), 143.5 (CH), 131.4 (C), 64.2 (C), 63.6 (CH), 63.1 (CH_2), 54.0 (CH), 41.1 (CH), 31.3 (CH_2), 20.8 (CH_3), 16.3 (CH_3). Anal. Calcd for $C_{14}H_{15}ClN_4O_3$: C, 52.10; H, 4.68; N, 17.36. Found: C, 49.87; H, 4.71; N, 17.02.

4.1.6. Acetic acid (1*S*,2*R*,4*R*,5*R*)-4-(6-amino-9*H*-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-ylmethyl ester (+)-8. Epoxide (−)-**6** (450 mg, 2.4 mmol) was converted to the protected adenosine carbanucleoside (+)-**8** (462 mg, 63%) as a white solid, according to the same procedure used in the preparation of (+)-**7** except stirring 12 h at rt then 4 h at 40 °C. Mp 137 °C (dec). $[\alpha]_D^{25}$ +16.2 (*c* 1, $CHCl_3$). IR (KBr): ν 3276, 3089, 1741, 1249 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H), 8.09 (s, 1H), 6.30 (br s, 2H), 5.09 (t, *J*=8.6 Hz, 1H), 4.27 and 4.19 (ABX, *J*=11.1, 6.5, 6.2 Hz, 2H), 3.56 (s, 1H), 2.49–2.32 (m, 2H), 2.03 (s, 3H), 1.53 (s, 3H), 1.47–1.35 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7 (C), 155.7 (C), 152.9 (CH), 149.9 (C), 138.6 (CH), 119.2 (C), 63.9 (C), 63.8 (CH), 63.3 (CH_2), 53.3 (CH), 41.0 (CH), 31.2 (CH_2), 20.8 (CH_3), 16.3 (CH_3). Anal. Calcd for $C_{14}H_{17}N_5O_{23}$: C, 55.44; H, 5.65; N, 23.09. Found: C, 55.72; H, 5.61; N, 23.05.

4.1.7. ((1*S*,2*R*,4*R*,5*R*)-4-(6-chloro-9*H*-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl)methanol (+)-10. A solution of (+)-**7** (200 mg, 0.62 mmol) and saturated methanolic ammonia (10 mL) was stirred in a flask fitted with a rubber stopper at rt for 10 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography using a gradient of petroleum ether/ethyl acetate as the eluent to give the 6-chloropurine carbanucleoside (+)-**10** (151 mg, 87%) as a white solid. Mp 65 °C. $[\alpha]_D^{25}$ +16.4 (*c* 1, $CHCl_3$). IR (KBr): ν 3321, 3271, 1237 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.69 (s, 1H), 8.44 (s, 1H), 5.19 (ddd, *J*=9.1, 8.0, 1.0 Hz, 1H), 3.91 and 3.85 (ABX, *J*=10.9, 5.5, 5.3 Hz, 2H), 3.58 (d, *J*=0.8 Hz, 1H), 2.46–2.32 (m, 1H), 1.58 (s, 3H), 1.58–1.53 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.8 (CH), 151.7 (C), 150.9 (C), 143.7 (CH), 131.3 (C), 64.9 (C), 63.4 (CH), 61.5 (CH_2), 54.3 (CH), 43.7 (CH), 30.7 (CH_2), 16.3 (CH_3). Anal. Calcd for $C_{12}H_{13}ClN_4O_2$: C, 51.34; H, 4.67; N, 19.96. Found: C, 51.65; H, 4.63; N, 20.01.

4.1.8. ((1*S*,2*R*,4*R*,5*R*)-4-(2-Amino-6-chloro-9*H*-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl)methanol (−)-11. Epoxide (−)-**6** (450 mg, 2.42 mmol) was converted to the protected 2-amino-6-chloropurine carbanucleoside **9**, according to the same procedure used in the preparation of (+)-**8**. Derivative **9** was contaminated with triphenylphosphine oxide, which will be eliminated during the next ammonia deprotective step. Derivative **9** was converted to 2-amino-6-chloropurine carbanucleoside (−)-**11**, according to the same procedure used in the preparation of (+)-**10**. At this stage, triphenylphosphine oxide present with **9** was conveniently eliminated by column chromatography to give pure (−)-**11** as a white foam (51% yield, two steps from (−)-**6**). $[\alpha]_D^{25}$ −2.5 (*c* 1, MeOH). IR (neat): ν 3305, 3172, 1676, 1615 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 8.05 (s, 1H), 6.87 (br s, 2H), 4.82 (t, *J*=8.4 Hz, 1H), 4.63 (t, *J*=5.0 Hz, 1H), 3.67 (s, 1H), 3.65 (partially overlapped ddd, *J*=11.5, 5.7, 5.0 Hz, 1H), 3.43 (ddd, *J*=10.5, 5.1, 5.0 Hz, 1H), 2.30–2.14 (m, 2H), 1.45 (s, 3H), 1.29–1.17 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.9 (C), 154.2 (C), 149.7 (C), 140.8 (CH), 123.4 (C), 64.5 (C), 63.5 (CH), 61.0 (CH_2), 53.8 (CH), 43.7 (CH), 30.4 (CH_2), 16.7

(CH_3). Anal. Calcd for $C_{12}H_{14}ClN_5O_2$: C, 48.74; H, 4.77; N, 23.68. Found: C, 49.03; H, 4.73; N, 23.71.

4.1.9. ((1*S*,2*R*,4*R*,5*R*)-4-(6-(Cyclopropylamino)-9*H*-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl)methanol (+)-1a. A mixture of (+)-**10** (200 mg, 0.712 mmol) and cyclopropylamine (1 mL) in dry THF (10 mL) was stirred at rt for 3 h, and the reaction mixture was evaporated in vacuo. The resulting residue was purified by column chromatography using gradients methylene chloride/methanol as the eluent to give the corresponding 6-cyclopropylamino carbanucleoside (+)-**1a** (198 mg, 92%) as a white foam. $[\alpha]_D^{25}$ +24.7 (*c* 1, $CHCl_3$). IR (neat): ν 3298, 3121, 1662 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.05 (s, 1H), 6.35 (br s, 1H), 5.09 (t, *J*=8.2 Hz, 1H), 3.86 (m, 2H), 3.54 (s, 1H), 3.01 (br s, 1H), 2.33 (m, 2H), 1.56 (s, 3H), 1.55–1.42 (m, 1H), 0.90 (m, 2H), 0.62 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8 (C), 153.2 (CH), 149.0 (C), 138.1 (CH), 119.4 (C), 64.5 (C), 63.7 (CH), 61.5 (CH_2), 53.5 (CH), 43.8 (CH), 30.7 (CH_2), 23.7 (CH), 16.3 (CH_3), 7.3 (2×CH_2). Anal. Calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 23.24. Found: C, 60.02; H, 6.39; N, 23.02.

4.1.10. ((1*S*,2*R*,4*R*,5*R*)-4-(6-Amino-9*H*-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]hex-2-yl)methanol (+)-1b. A solution of (+)-**8** (200 mg, 0.66 mmol) and saturated methanolic ammonia (10 mL) was stirred in a flask fitted with a rubber stopper at rt for 10 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography using gradients petroleum ether/ethyl acetate as the eluent to give adenosine carbanucleoside (+)-**1b** (157 mg, 91%) as a white solid. Mp 162 °C. ee=99%, determined by chiral HPLC (Chiralcel OD-H, hexane/2-PrOH 9:1, 1 mL/min, UV and CD detection at 254 nm, 25 °C, Rt(+)=21.37, Rt(−)=25.09, k(+)=6.01, k(−)=7.23, alpha=1.20 and Rs=1.36). $[\alpha]_D^{25}$ +26.9 (*c* 1, MeOH/$CHCl_3$ 1:1). IR (KBr): ν 3273, 3109, 1671 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 8.15 (s, 1H), 8.11 (s, 1H), 7.26 (br s, 2H), 4.99 (t, *J*=8.2 Hz, 1H), 4.67 (t, *J*=4.9 Hz, 1H), 3.70 (s, 1H), 3.67 (td, *J*=10.2, 5.8 Hz, 1H), 3.47 (td, *J*=10.2, 5.8 Hz, 1H), 2.34–2.22 (m, 2H), 1.48 (s, 3H), 1.29 (dt, *J*=11.8, 8.9 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 156.2 (C), 152.7 (CH), 149.7 (C), 138.5 (CH), 118.8 (C), 64.5 (C), 63.8 (CH), 61.0 (CH_2), 53.7 (CH), 43.8 (CH), 30.7 (CH_2), 16.8 (CH_3). Anal. Calcd for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 55.32; H, 5.83; N, 26.99.

4.1.11. ((1*S*,2*R*,4*R*,5*R*)-4-(2-Amino-6-(cyclopropylamino)-9*H*-purin-9-yl)-1-methyl-6-oxa-bicyclo[3.1.0]-hexan-2-yl)methanol (+)-1c. Derivative (−)-**11** was converted to the 2-amino-6-cyclopropylamino carbanucleoside (155 mg, 83%) as a white foam (+)-**1c**, according to the same procedure used in the preparation of (+)-**1a** except stirring at 50 °C for 2 h. $[\alpha]_D^{25}$ +12.7 (*c* 1, MeOH/$CHCl_3$ 1:1). IR (neat): ν 3299, 3185, 1668 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 7.66 (s, 1H), 7.30 (br d, *J*=4.82 Hz, 1H), 5.82 (br s, 2H), 4.75 (ddd, 9.3, 8.3, 1.0 Hz, 1H), 4.63 (t, *J*=5.1 Hz, 1H), 3.64 (ddd, *J*=11.9, 6.2, 5.8 Hz, 1H), 3.61 (d, *J*=0.8 Hz, 1H), 3.44 (ddd, *J*=10.7, 6.0, 5.1 Hz, 1H), 3.03 (br s, 1H), 2.29–2.06 (m, 2H), 1.45 (s, 3H), 1.18 (dt, *J*=12.0, 9.3 Hz, 1H), 0.68–0.61 (m, 2H), 0.59–0.53 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.4 (C), 156.1 (C), 151.5 (C), 134.7 (CH), 113.4 (C), 64.2 (C), 63.8 (CH), 61.0 (CH_2), 52.9 (CH), 43.7 (CH), 30.7 (CH_2), 24.0 (CH), 16.8 (CH_3), 6.6 (2×CH_2). Anal. Calcd for $C_{15}H_{20}N_6O_2$: C, 56.95; H, 6.37; N, 26.56. Found: C, 57.29; H, 6.41; N, 26.67.

Acknowledgements

We are thankful to Dr. R. Faure for NOESY and HMBC experiments. We thank P. Fournier for the English language revision of the manuscript.

References and notes

1. (a) Agrofolio, L. A.; Challaud, S. R. *Acyclic, Carbocyclic and L-Nucleosides*; Kluwer Academic: Dordrecht, Boston, London, 1998; Recent reviews: (b) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229–9272; (c) Ferrero, M.; Gotor, V. *Chem. Rev.* **2000**, *100*, 4319–4348; (d) Rodriguez, J. B.; Comin, M. J. *Mini-Rev. Med. Chem.* **2003**, *3*, 95–114.
2. (a) Herdewijn, P.; De Clercq, E.; Balzarini, J.; Vanderhaeghe, H. *J. Med. Chem.* **1985**, *28*, 550–555; (b) Marquez, V. E.; Lim, M. *Med. Res. Rev.* **1986**, *6*, 1–40; (c) Roberts, S.; Biggadike, K.; Borthwick, A. D.; Kirk, B. *Topics in Medicinal Chemistry*; Leeming, P. R., Ed.; Royal Society of Chemistry: London, 1988; (d) Saunders, J.; Cameron, J. M. *Med. Res. Rev.* **1995**, *15*, 497–531.
3. For selected recent syntheses and references cited therein see: (a) Moon, H. R.; Lee, H. J.; Kim, K. R.; Lee, K. M.; Lee, S. K.; Kim, H. O.; Chun, M. W.; Jeong, L. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5641–5644; (b) Kim, J. W.; Choi, B. G.; Hong, J. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1812–1816; (c) Zhu, X.-F.; Nydegger, F.; Gossauer, A. *Helv. Chim. Acta* **2004**, *87*, 2245–2265; (d) Gonzalez-Moa, M. J.; Besada, P.; Teijeira, M.; Teran, C.; Uriate, E. *Synthesis* **2004**, 543–548; (e) Quadrelli, P.; Scrocchi, R.; Caramella, P.; Rescifina, A.; Piperno, A. *Tetrahedron* **2004**, *60*, 3643–3651; (f) Yang, Y.-Y.; Meng, W.-D.; Qing, F.-L. *Org. Lett.* **2004**, *6*, 4257–4259; (g) Hegedus, L. S.; Cross, J. *J. Org. Chem.* **2004**, *69*, 8492–8495; (h) Wang, J.; Jin, Y.; Rapp, K. L.; Bennett, M.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2005**, *48*, 3736–3748; (i) Meillon, J.-C.; Griffe, L.; Storer, R.; Gosselin, G. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 695–699; (j) García, M. D.; Caamaño, G.; Fernández, F.; Lopez, C.; De Clercq, E. *Synthesis* **2005**, 925–932; (k) Lee, J. A.; Moon, H. R.; Kim, H. O.; Kim, K. R.; Lee, K. M.; Kim, B. T.; Hwang, K. J.; Chun, M. W.; Jacobson, K. A.; Jeong, L. S. *J. Org. Chem.* **2005**, *70*, 5006–5013; (l) Roy, A.; Schneller, S. W.; Keith, K. A.; Hartline, C. B.; Kern, E. R. *Bioorg. Med. Chem.* **2005**, *13*, 4443–4449; (m) Jin, Y. L.; Hong, J. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1366–1368; (n) Oh, C. H.; Hong, J. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1520–1524; (o) Kim, A.; Hong, J. H. *Bull. Korean Chem. Soc.* **2005**, *26*, 1767–1770; (p) Jiang, M. X.-W.; Jin, B.; Gage, J. L.; Priour, A.; Savela, G.; Miller, M. J. *J. Org. Chem.* **2006**, *71*, 4164–4169; (q) Ludek, O. R.; Krämer, T.; Balzarini, J.; Meier, C. *Synthesis* **2006**, 1313–1324; (r) García, M. D.; Caamaño, O.; Fernández, F.; Abeijon, P.; Blanco, J. M. *Synthesis* **2006**, 73–80; (s) Gosselin, G.; Griffe, L.; Meillon, J.-C.; Storer, R. *Tetrahedron* **2006**, *62*, 906–914.
4. (a) Comin, M. J.; Rodriguez, J. B.; Russ, P.; Marquez, V. E. *Tetrahedron* **2003**, *59*, 295–301; (b) Paoli, L.; Piccini, S.; Rodriguez, M.; Sega, A. *J. Org. Chem.* **2004**, *69*, 2881–2883; (c) Ishikura, M.; Matsumoto, K.; Murakami, A. *Heterocycles* **2004**, *64*, 241–248.

5. (a) Kim, H. S.; Ohno, M.; Xu, B.; Kim, H. O.; Choi, Y.; Ji, X. D.; Maddileti, S.; Marquez, V. E.; Harden, T. K.; Jacobson, K. A. *J. Med. Chem.* **2003**, *46*, 4974–4987; (b) Choi, Y.; George, C.; Comin, M. J.; Barchi, J. J., Jr.; Kim, H. S.; Jacobson, K. A.; Balzarini, J.; Mitsuya, H.; Boyer, P. L.; Hughes, S. H.; Marquez, V. E. *J. Med. Chem.* **2003**, *46*, 3292–3299; (c) Choi, Y.; Moon, H. R.; Yoshimura, Y.; Marquez, V. E. *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 547–557; (d) Kim, K. W.; Hong, J. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 668–672; (e) Moon, H. R.; Kim, K. R.; Kim, B. T.; Hwang, K. J.; Chun, M. W.; Jeong, L. S. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 709–711; (f) Tchilibon, S.; Joshi, B. V.; Kim, S.-K.; Duong, H. T.; Gao, Z.-G.; Jacobson, K. A. *J. Med. Chem.* **2005**, *48*, 1745–1758; (g) Marquez, V. E.; Choi, Y.; Comin, M. J.; Russ, P.; George, C.; Huleihel, M.; Ben-Kasus, T.; Agbaria, R. *J. Am. Chem. Soc.* **2005**, *127*, 15145–15150; (h) Joschi, B. V.; Moon, H. R.; Fettinger, J. C.; Marquez, V. E.; Jacobson, K. A. *J. Org. Chem.* **2005**, *70*, 439–447; (i) Comin, M. J.; Parrish, D. A.; Deschamps, J. R.; Marquez, V. E. *Org. Lett.* **2006**, *8*, 705–708.
6. Koole, L. H.; Neidle, S.; Crawford, M. D.; Krayevski, A. A.; Gurskaya, G. V.; Sandström, A.; Wu, J.-C.; Tong, W.; Chattopadhyaya, J. *J. Org. Chem.* **1991**, *56*, 6884–6892.
7. Aubin, Y.; Audran, G.; Monti, H. *Synlett* **2006**, 2215–2218.
8. (a) Wang, P.; Gullen, B.; Newton, M. G.; Cheng, Y. C.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **1999**, *42*, 3390–3399; (b) Wang, P.; Agrofolio, L. A.; Newton, H. G.; Chu, C. K. *J. Org. Chem.* **1999**, *64*, 4173–4178; (c) Bondada, L.; Gumina, G.; Nair, R.; Ning, X. H.; Shinazi, R. F.; Chu, C. K. *Org. Lett.* **2004**, 2531–2534.
9. (a) Balzarini, J.; Baumgartner, H.; Bodenteich, H.; Declercq, E.; Griengl, H. *J. Med. Chem.* **1989**, *32*, 1861–1865; (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551–554.
10. In this note, numbering of products is given by analogy with the parent nucleosides.
11. Audran, G.; Acherar, S.; Monti, H. *Eur. J. Org. Chem.* **2003**, 92–98.
12. Embest, H. B.; Wilson, A. *J. Chem. Soc.* **1957**, 1958–1965.
13. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Jenny, T. F.; Horlacher, J.; Previsani, N.; Benner, S. A. *Helv. Chim. Acta* **1992**, *75*, 1944–1954; (c) Review: Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127–164.
14. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, NY, 1999; pp 150–157.