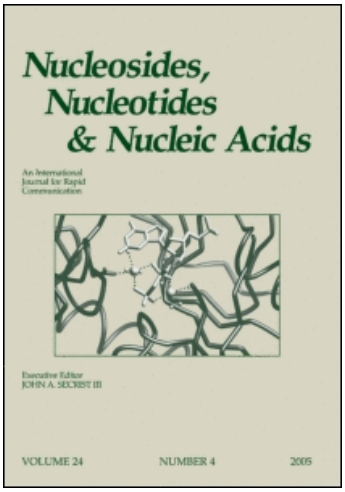

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Synthetic and Antiviral Studies of Carboacyclic 6- and 2,6-Substituted Purine Nucleosides

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To cite this Article Pontikis, Renée and Monneret, Claude(1993) 'Synthetic and Antiviral Studies of Carboacyclic 6- and 2,6-Substituted Purine Nucleosides', Nucleosides, Nucleotides and Nucleic Acids, 12: 5, 547 — 558
To link to this Article: DOI: 10.1080/07328319308021222
URL: http://dx.doi.org/10.1080/07328319308021222

NUCLEOSIDES & NUCLEOTIDES, 12(5), 547-558 (1993)

SYNTHETIC AND ANTIVIRAL STUDIES OF CARBOACYCLIC 6- AND 2,6-SUBSTITUTED PURINE NUCLEOSIDES

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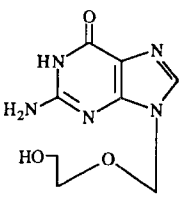
Abstract. Chiral purine derivatives containing a carboacyclic chain mimicking the ribose ring, but lacking the C(3')-C(4') bond have been prepared from (2*S*,3*R*)-3-amino-1,2,6-tribenzyloxyhexane **15.** The synthesis of this amine *via* an hex-2-enopyranoside utilizes the absolute configuration defined by carbons 4 and 5 of D-glucose. None of these compounds exhibited any antiviral activity against HIV.

INTRODUCTION

Since the discovery of Acyclovir **1** as potent antiviral[1], a large variety of acyclic analogs of nucleosides have been synthesized[2] and some of these compounds have been shown to possess significant antiviral effects. Thus Acyclovir **1**, DHPG (Ganciclovir) **2** and its carbon isoster BRL 39123 (Penciclovir) **3** exhibit potent and selective activity against *Herpes simplex* virus[3,4], whereas enantiomer S of DHPA **4** inhibited the replication of a number of DNA and RNA viruses[5]. Moreover, Ganciclovir, which is also a powerful inhibitor of human cytomegalovirus (HCMV) is used clinically in immuno-compromised patients[6].



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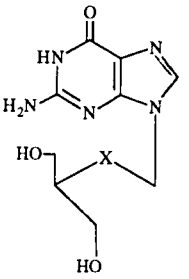
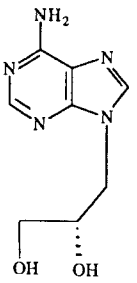


2 X=O

3 X=CH_2



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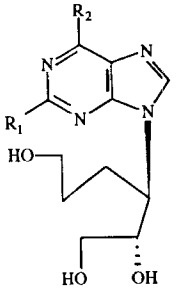
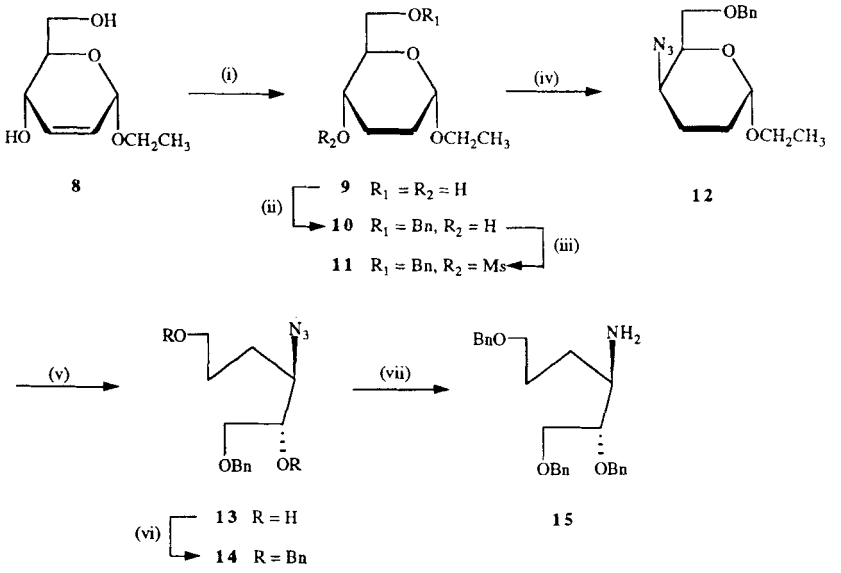
The importance of chirality for antiviral activity was clearly demonstrated with certain acyclic purine analogues, where only one enantiomer points to a greater activity[5,7]. Thus, as a part of our continuing efforts in the search of acylic nucleosides as potential antiviral agents[8], we have undertaken the synthesis of some carboacyclic compounds for which the carbon bearing the nucleobase was chiral[9-11].

We report here the study of a series of 6- or 2,6-substituted purine nucleoside analogues (**5**, **6**, **7**) containing a ribo configurated carbocyclic moiety but lacking the C(3')-C(4') bond.



R_2	R_1 = H	R_1 = NH_2
Cl	**5a**	**5b**
OH	**6a**	**6b**
NH_2	**7a**	**7b**

The synthesis of these desired purine derivatives followed a standard route in the field of carbocyclic nucleosides[12]. This involved construction, first of a primary amine containing the correct stereochemical configurations, and then introduction of the amine into the heterocyclic base portion of the molecule.



Scheme 1:

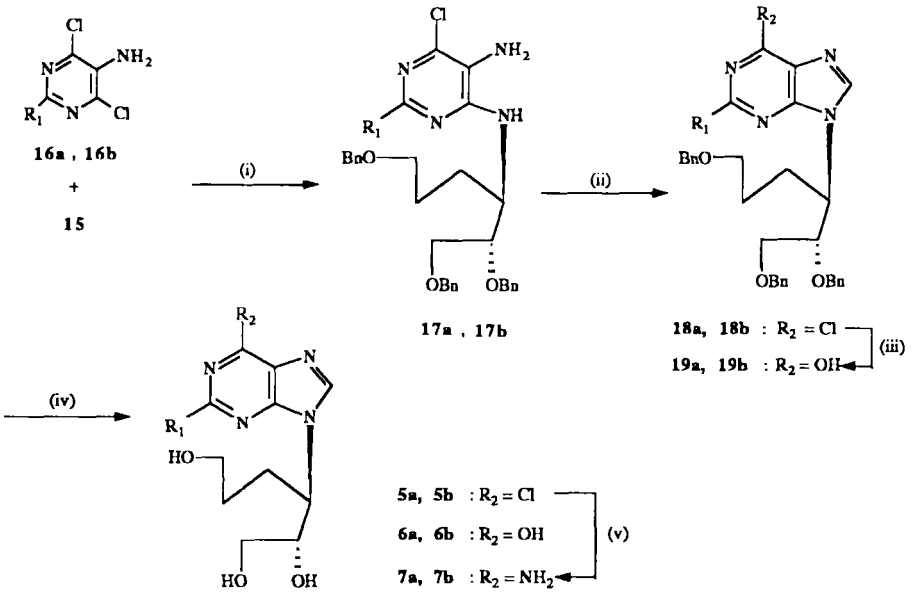
(i) H_2, Pd/C, Et_3N, EtOH, 4h; (ii) Bu_2SnO, Bz, reflux, 17h then Bu_4NI, BnBr, reflux, 48h; (iii) MsCl, Et_3N, CH_2Cl_2, 0°C, 1h; (iv) NaN_3, DMF, 100°C, 30h; (v) a) AcOH, H_2O, 90°C, 6h, b) $NaBH_4$, MeOH, 0°C, 1h; (vi) NaH, THF, 0°C, 10 min then Bu_4NI, BnBr, 1.5h; (vii) H_2, Pd/C, Et_3N, MeOH, 5h.

CHEMISTRY

The stereospecific synthesis of amine **15** which started from the readily available diol **8** (44 % overall yield), utilized the absolute configuration defined by carbons 4 and 5 of D-glucose (Scheme 1)

Ethyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **8**, prepared from tri-O-acetyl-D-glucal using Ferrier's reaction[13], provided, after catalytic hydrogenation, the saturated glycoside **9**. The primary hydroxy group of **9** was protected as a benzyl ether *via* selective activation with dibutyltin oxide[14]. After mesylation of the resulting compound **10**, treatment of **11** with sodium azide yielded the azido-sugar **12** of configuration *threo*. Mild acid hydrolysis of **12** and subsequent reduction afforded the diol **13** (89 %). Finally benzylation of **13**, followed by catalytic hydrogenation, led to the desired amine **15**.

Therefore, the amine **15** was condensed with 5-amino-4,6-dichloropyrimidine **16a** in *n*-butanol by refluxing, in presence of triethylamine, to give the corresponding



Scheme 2 (derivatives **a** : R_1=H, derivatives **b** : R_1=NH_2)

(i) Et_3N, *n*BuOH, reflux, 48h; (ii) $(EtO)_3CH$, HCl cat, DMA, 18h; (iii) 1N HCl, EtOH, reflux, 9h; iv) BBr_3, CH_2Cl_2, -78°C, 1h; (v) NH_3, MeOH, 90°C, 5h.

pyrimidinylamino derivative **17a** (Scheme 2). Ring closure, with triethyl orthoformate in the presence of a catalytic amount of concentrated hydrochloric acid, provided the 6-chloropurine analogue **18a**.

Similarly, condensation of **15** with 2,5-diamino-4,6-dichloropyrimidine **16b**[15] afforded the triamino pyrimidine derivative **17b** which was converted into the 2-amino-6-chloropurine derivative **18b** by ring closure, as above, and subsequent mild acid hydrolysis to remove the N-formate formed during the reaction.

Hydrolysis of the 6-chloro moieties in **18a** and **18b,** by refluxing in ethanolic chlorhydric acid, provided the hypoxanthine **19a** and guanine **19b** nucleoside analogues, respectively. Debenzylation of the four compounds **18a**, **18b**, **19a** and **19b** with boron tribromide [16] in methylene chloride at -78°C afforded the four corresponding triols. Access to the 6-amino structures was obtained by displacement of the halide in **5a** and **5b** with saturated methanolic ammonia to yield the adenine and the 2,6-diaminopurine derivatives **7a** and **7b**, respectively.

BIOLOGICAL RESULTS

All the new purine derivatives prepared in this study (**5**, **6**, **7**) were evaluated for their protective activity against cytopathogenic effects produced by strain Lav of HIV replicating in CEM cells. At concentations up to 3 x 10^{-4} mg/mL, all the compounds were found inactive against HIV replication (Rhône-Poulenc Rorer).

EXPERIMENTAL PART

Melting points were determined using a Reichert Thermovar apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. UV spectra were determined on a Varian-Techtron spectrophotometer. IR spectra were obtained with a Perkin-Elmer 1710 spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker AC-250 spectrometer, and chemical shifts are recorded in parts per million downfield from internal tetramethylsilane (s = singulet, d = doublet, dd = double doublet, t = triplet, bs = broad singulet, m = multiplet). Mass spectra were recorded under chemical ionization (CI) conditions on a Nermag R 10.10C and high-resolution mass spectra (HRMS) on a AEI MS instruments. Elemental analyses were performed by the Service de Microanalyse du CNRS, Division de Vernaison, France. The thin-layer chromatographic analyses were performed using precoated silica gel G (F) plates and the spots were examined with UV light and phosphomolybdic acid spray. Column chromatography were carried out on Merck silica gel 60 (230-240 mesh).

Ethyl 2,3-dideoxy-α–D-erythro-hexopyranoside **9** :

An ethanolic solution (50 mL) of **8**[13] (3.0 g, 17.2 mmol) was stirred for 4 h under an hydrogen atmosphere (1 atm.) in the presence of triethylamine (3 mL) and 5% palladium-on-charcoal (400 mg). After filtration to remove the catalyst the solvent was evaporated under reduced pressure. Column chromatography (ethyl acetate-methanol, 98:2) of the residue afforded **9** (2.58 g, 85%): m.p. 73°C; $[\alpha]_D$ +127° (*c*, 1.0 MeOH); IR ($CHCl_3$) ν_{max} 3400, 3300 (OH) cm^{-1}; ^{1} H NMR ($CDCl_3$, 250 MHz) δ 1.22 (t, 3H, J = 7 Hz, CH_3), 1.83 (m, 4H, CH_2-2 and CH_2-3), 2.28 (bs, 2H, OH x 2), 3.44 and 3.71 (2 q each, 1H each, J = 10, 7 Hz, CH_2CH_3), 3.59 (m, 2H, CH_2-6), 3.81 (bs, 2H, H-4 and H-5), 4.80 (bd,1H, J = 3 Hz, H-1); MS (CI, NH3) *m/z* 194 $(M + NH_4)^+$, 177 $(M + H)^+$, 148 $(M + NH_4 - EtOH)^+$, 131 $(M + H - EtOH)^+$.

Ethyl 6-O-benzyl-2,3-dideoxy-α–D-erythro-hexopyranoside **10** :

A mixture of the glycoside **9** (3.08 g, 17.5 mmol) and dibutyltin oxide (4.36 g, 17.5 mmol) in benzene (350 mL) was refluxed for 15 h with azeotropic removal of water. After cooling tetra-*n*-butylammonium bromide (6.46 g, 17.5 mmol) and benzyl bromide (3.1 mL, 26 mmol) were added. The mixture was heated under reflux for 50 h and then

was concentrated under reduced pressure. The residue was subject to column chromatography (cyclohexane-ethyl acetate, 1:1, Rf 0.32) to give **10** (3.72 g, 82 %) as an oil; $[\alpha]_D$ + 87° (*c* 1.1 $CHCl_3$); IR ($CHCl_3$) ν_{max} 3605, 3505 (OH) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (t, 3H, J = 7 Hz, CH_3),1.80 (m, 4H, CH_2-2 and CH_2-3), 2.60 (d, 1H, J = 2.5 Hz, OH), 3.44 (2 q, 1H, J = 10, 7 Hz, C*H*HCH_3,), 3.60 - 3.75 (m, 5H, C*H*HCH_3, H-4, H-5, CH_2-6), 4.56 and 4.63 (2 d, 1H each, J gem = 12 Hz, CH_2Ph), 4.79 (bd, 1H, J = 3 Hz, H-1), 7.34 (s, 5H, Ph).

Ethyl 4-azido-6-O-benzyl-2,3-dideoxy-α-D-threo-hexopyranoside **12** :

To a stirred and ice-cooled solution of **10** (3.33 g, 12.5 mmol) in anhydrous dichloromethane (100 mL) were successively added triethylamine (2.1 mL, 15 mmol) and mesyl chloride (1.1mL, 14.2 mmol). After stirring for 1 h at 0°C, water was added (50 mL), the organic phase was separated, dried then concentrated to afford the corresponding mesylate **11**, as an oil (4.30 g), which was reacted further without purification. A solution of the crude mesylate in DMF (60 mL) was stirred with sodium azide (1.22 g, 18.7 mmol) at 100°C for 24 h. Then water (150 mL) was added and the product extracted with diethyl ether (200 mL x 2). The combined ether extracts were washed with brine, dried ($MgSO_4$), concentrated and subject to column chromatography (cyclohexane-ethyl acetate, 9 : 1) to give **12** as a colorless oil (2.84 g, 78 %); $[\alpha]_D$ +36° (*c* 1.1 $CHCl_3$); Anal. calc for $C_{15}H_{21}N_3O_3$: C 61.83, H 7.27, N 14.42. Found : C 61.26, H 7.28, N 14.28; IR ($CHCl_3$) ν_{max} 2105 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.22 (t, 3H, J = 7 Hz, CH_3), 1.85-2.25 (m, 4H, CH_2-2and CH_2-3), 3.46 and 3.71 (2 q each, 1H each, J = 10, 7 Hz, CH_2CH_3), 3.55 (m, 2H, H-6), 3.75 (m, 1H, H-4), 4.07 (t, 1H, J = 6.5Hz, H-5), 4.53 and 4.59 (2d, 1H each, J gem = 11.5 Hz, CH_2Ph), 4.85 (d, 1H, J = 2.5 Hz, H-1), 7.36 (s, 5H, Ph); MS *m/z* 309 $(M + NH_4)^+$, 263 $(M + NH_4 - EtOH)^+$.

(2 S, 3R)-3-Azido-1-benzyloxy-2,6-dihydroxyhexane **13** :

A solution of **12** (2.61 g, 8.9 mmol) in 80 % aqueous acetic acid (25 mL) was heated at 90°C for 6 h. After cooling the solvent was evaporated to low volume and reevaporated following the addition of toluene to give a syrup [2.3 g; IR ($CHCl_3$) ν_{max} 3593, 3435 (OH), 2111 (N_3) cm^{-1}]. To this crude product, in solution in 100 mL of dry methanol, sodium borohydride (335 mg, 8.9 mmol) was added portionwise at 0°C. After stirring for 1 h at 0°C the mixture was neutralized with 25 % aqueous acetic acid, poured into water and extracted with dichloromethane. The organic phases were dried ($MgSO_4$), concentrated and subjected to column chromatography (cyclohexane-ethyl acetate, 1:1) to afford **13** (2.11 g, 89 %) as an oil; $[\alpha]_D$ -18° (*c* 1.0 $CHCl_3$); IR ($CHCl_3$) ν_{max} 3624, 3570 (OH), 2109 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.65-1.80 (m, 4H, CH_2-

4, CH_2-5), 2.10 (s, 2H, OH x 2), 3.38 (m 1H, H-3), 3.56 (d, 2H, J = 5.5 Hz, CH_2-1), 3.68 (m, 2H, CH_2-6), 3.84 (m, 1H, H-2), 4.56 (s, 2H, *CH_2*Ph), 7.34 (s, 5H, Ph); MS *m/z* 283 $(M + NH_4)^+$, 266 $(M + H)^+$, 238 $(M + H - 28)^+$.

(2S, 3R)-3-Azido-1,2,6-tribenzyloxyhexane **14** :

To an ice-cooled suspension of previously washed (THF) sodium hydride (60 % oil dispersion, 760 mg, 19 mmol) in dry tetrahydrofuran (20 mL) under argon was added dropwise **13** (2.0 g, 7.55 mmol) in tetrahydrofuran (25 mL). After stirring for 30 min at 0° C tetra-*n*-butylammonium iodide (560 mg, 1.51 mmol) and benzyl bromide (2.0 mL, 16.8 mmol) were added successively. The reaction mixture was stirred at room temperature for 2 h, quenched with water (40 mL), extracted with diethyl ether (50 mL x 2). The organic phase was washed with water (50 mL), dried ($MgSO_4$) and evaporated. Purification by chromatography (cyclohexane-ethyl acetate, 8:2) afforded **14** as a colorless oil (2.75 g, 82 %); $[\alpha]_D$ + 0.7° (*c* 1.0 $CHCl_3$); Anal. calc. for $C_{27}H_{31}N_3O_3$: C 72.78, H 7.01, N 9.43. Found : C 72.86, H 7.07, N 9.51; IR ($CHCl_3$) ν_{max} 2107 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.55-1.85 (m, 4H, CH_2-4, CH_2-5), 3.46 (m, 3H, H-3, CH_2-6), 3.63 (m, 3H, H-2, CH_2-1), 4.49 (s, 2H, *CH_2*Ph), 4.51 and 4.56 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 4.60 and 4.77 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 7.33 (s, 15H, Ph x 3); MS *m/z* 463 $(M + NH_4)^+$, 446 $(M + H)^+$, 418 $(M + H - 28)^+$.

(2S, 3R)-3-Amino-1,2,6-tribenzyloxyhexane **15** :

A mixture of **14** (1.52 g, 3.41 mmol), triethylamine (0.5 mL), 5% palladium on charcoal (67 mg) in methanol (50 mL) was hydrogenated for 5 h, filtered and concentrated. Column chromatography (dichloromethane-methanol, 95 : 5) of the residue yielded **15** (1.36 g, 95 %) as a colorless oil; $[\alpha]_D$ -14° (*c* 1.1 $CHCl_3$); Anal. calc. for $C_{27}H_{33}NO_3$ C 77.29, H 7.93, N 3.34. Found : C 77.25, H 8.03, N 3.46; IR ($CHCl_3$) 3380 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.30-1.80 (m, 4H, CH_2-4, CH_2-5), 1.52 (s, 2H, NH_2), 2.88 (m, 1H, H-3), 3.46 (m, 3H, H-2, CH_2-6), 3.66 (m, 2H, CH_2-1), 4.52 (d, 4H, J_{gem} = 12 Hz, *CH_2*Ph x 2), 4.55 and 4.75 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 7.33 (s, 15H, Ph x 3); MS *m/z* 420 $(M + H)^+$.

(2S,3R)-3-[(5-Amino-6-chloro-4-pyrimidinyl)-amino]-1,2,6-tribenzyloxyhexane **17a** :

A solution of **15** (1,2 g, 2.88 mmol), 5-amino-4,6-dichloropyrimidine (472 mg, 2.88 mmol), triethylamine (6 mL) and *n*-butanol (40 mL) was refluxed under argon for 48 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (diethyl ether-cyclohexane, 1:1; Rf 0.15) to afford the title compound **17a** (680 mg, 43 %) as an oil; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.58-1.90 (m, 4H, CH_2-4', CH_2-5'), 3.31 (s, 2H, NH_2), 3.48 (t, 2H, J = 5.5 Hz, CH_2-6'), 3.62 (m, 2H,

CH_2-1'), 3.81 (t, 1H, J = 5 Hz, H-2'), 4.45-4.60 (m, 5H, H-3', CH_2Ph x 2), 4.66 and 4.78 (2d, 2H, J_{gem} = 12 Hz, CH_2Ph), 5.30 (d, 1H, J = 9.5 Hz, NH), 7.31, 7.33, 7.34 (3s, 15H, Ph x 3), 8.02 (s, 1H, H-2); MS *m/z* 547 and 549 $(M + H)^+$, 513 $(M + H - Cl)^+$, 201.

(2S,3R)-3-[(2-5-Diamino-6-chloro-4-pyrimidinyl)-amino]-1,2,6-tribenzyloxyhexane **17b** ;

A solution of **15** (1,45 g, 3.46 mmol), 2,5-diamino-4,6-dichloropyrimidine (620 mg, 3.46 mmol) , triethylamine (6 mL) and *n*-butanol (45 mL) was refluxed for 48 h. It was processed as described in the above procedure to yield **17b** as an oil (800 mg, 41 %); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.55-1.75 (m, 4H, CH_2-4', CH_2-5'), 2.58 (s, 2H, NH_2), 3.45 (t, 2H, J = 6 Hz, CH_2-6'), 3.54 and 3.57 (2dd, 1H each, J = 9, 25 Hz, CH_2-1'), 3.74 (t, 1H, J = 6 Hz, H-2'), 4.38-4.52 (m, 7H, H-3', CH_2Ph x 2, NH_2), 4.61 and 4.76 (2d, 4H, J_{gem} = 12 Hz, CH_2Ph x 2), 5.58 (ld, 1H, J = 9.5 Hz, NH), 7.30, 7.32, 7.33 (3s, 15H, Ph); MS *m/z* 563 and 565 $(M + 2H)^+$, 392, 216.

(2S,3R)-3-(6-Chloro-9H-purin-9-yl)-1,2,6-tribenzyloxyhexane **18a** ;

To a solution of **17a** (380 mg, 0.70 mmol) in 8mL of anhydrous dimethylacetamide, 8 mL of freshly distilled triethyl orthoformate and 0.1 mL of concentrated HCl were added. The mixture was stirred under argon at room temperature for 18 h and then concentrated in vacuo to a brown residue which was subjected to column chromatography. Elution with dichloromethane-acetone, 95:5 (Rf 0.20) gave **18a** as a glass (323 mg, 83 %); $[\alpha]_D$ - 4° (*c* 1.1 $CHCl_3$); IR ($CHCl_3$) ν_{max} 2928, 2865 (CH), 1592, 1562 (C=C, C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25-1.50 (m, 2H, CH_2-5'), 1.99 and 2.24 (2m, 2H, CH_2-4') 3.30 (dd, 1H, J = 5.5, 10 Hz, CH_2-1'a), 3.36 (m, 2H, CH_2-6'), 3.49 (dd, 1H, J = 4.5, 10 Hz, CH_2-1'b), 4.00 (m, 1H, H-2'), 4.38 and 4.40 (2d, 1H each, J_{gem} = 11.5 Hz, CH_2Ph), 4.41 (s, 2H, CH_2Ph), 4.42 and 4.69 (2d, 1H each, J_{gem} = 11.5 Hz, CH_2Ph), 4.92 (m, 1H, H-3'), 7.28 (m, 15H, Ph x 3), 8.23 and 8.60 (2s, 1H x 2, H-2 and H-8); MS *m/z* 557 and 559 $(M + H)^+$, 523 $(M - Cl)^+$, 231.

(2S,3R)-3-(2-Amino-6-chloro-9H-purin-9-yl)-1,2,6-tribenzyloxyhexane **18b** ;

As above a mixture of **17b** (400 mg, 0.71 mmol), dimethylacetamide (8 mL), triethyl orthoformate (10 mL) and concentrated HCl (0.1 mL) was stirred for 24 h. The volatile materials were removed in vacuo. The residue was dissolved in dimethylacetamide (6 mL) and treated with concentrated HCl (0.3 mL) at room temperature for 15 h to hydrolyze the N-formyl derivative. After evaporation under reduced pressure the residue was stirred with methanolic ammonia (20 mL, 5 % NH_3) at room temperature for 6h. The solvent was removed *in vacuo* and the product was partitioned between water and dichloromethane. The organic layer was dried ($MgSO_4$), evaporated then purified by

column chromatography (dichloromethane-acetone, 92:8, Rf 0.28) to give **18b** (455 mg, 78 %) as a yellow glass; $[\alpha]_D$ -3° (*c* 1.2 $CHCl_3$); IR ($CHCl_3$) ν_{max} 3531, 3422 (NH_2), 2927, 2866 (CH), 1607, 1567 (C=C, C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25-1.55 (m, 2H, CH_2-5'), 1.97 and 2.17 (2m, 2H, CH_2-4'), 3.28 (dd, 1H, J = 6.5, 10 Hz, CH_2-1'a), 3.41 (m, 2H, CH_2-6'), 3.53 (dd, 1H, J = 5, 10 Hz, CH_2-1'b), 3.98 (m, 1H, H-2'), 4.44 (s, 2H, *CH_2*Ph), 4.47 (s, 2H, *CH_2*Ph), 4.52 and 4.75 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 4.77 (m, 1H, H-3'), 4.95 (s, 2H, NH_2), 7.30 (m, 15H, Ph x 3), 7.96 (s, 1H, H-8); MS *m/z* 572 and 574 $(M + H)^+$, 392.

9-[(2S,3R)-1,2,6-Tribenzyloxy-*n*-hex-3-yl]-hypoxanthine **19a** :

A solution of **18a** (185 mg, 0.33 mmol) and hydrochloric acid (1 N, 2.5 mL) in ethanol (6 mL) was boiled under reflux for 9 h. The ethanol was evaporated in vacuo and the aqueous solution was neutralized with 1 N NaOH, then extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated to dryness. The residue was purified by column chromatography (dichloromethane-methanol, 94:6, Rf 0.24) to yield **19a** (139 mg, 78 %) as a white amorphous solid; $[\alpha]_D$ + 8.5° (*c* 1.0 $CHCl_3$); IR ($CHCl_3$) ν_{max} 2956, 2867 (CH), 1687 (C=O), 1589 (C=C, C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.30 (m, 2H, CH_2-5'), 1.90 and 2.10 (2m, 2H, CH_2-4') 3.30 (m, 3H, CH_2-1'a, CH_2-6'), 3.41 (dd, 1H, J = 5, 10 Hz, CH_2-1'b), 3.92 (m, 1H, H-2'), 4.28 and 4.35 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 4.35 (s, 2H, *CH_2*Ph), 4.40 and 4.65 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 4.84 (m, 1H, H-3'), 7.20 (m, 15H, Ph x 3), 8.14 and 8.45 (2s, 1H x 2, H-2 and H-8), 12.0 (bs, 1H, NH); MS *m/z* 539 $(M + H)^+$.

9-[(2S,3R)-1,2,6-Tribenzyloxyhex-3-yl]-guanine **19b** :

A mixture of **18b** (150 mg, 0.26 mmol), 1N HCl (3 mL) and ethanol (5 mL) was treated as described for compound **19a**. Purification by column chromatography (dichloromethane-methanol, 9:1, Rf 0.31) afforded **19b** as a white amorphous solid (98 mg, 67 %); $[\alpha]_D$ + 9° (*c* 1.1 $CHCl_3$); IR ($CHCl_3$) ν_{max} 3485, 3303(NH_2), 2930, 2860 (CH), 1688 (C=O), 1605 (C=C, C=N) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.44 (m, 2H, CH_2-5'), 1.98 and 2.14 (2m, 2H, CH_2-4'), 3.42 (m, 3H, CH_2-1'a, CH_2-6'), 3.55 (dd, 1H, J = 3.5, 10 Hz, CH_2-1'b), 4.00 (m, 1H, H-2'), 4.43 and 4.50 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 4.49 (s, 2H, *CH_2*Ph), 4.54 and 4.79 (2d, 1H each, J_{gem} = 12 Hz, *CH_2*Ph), 4.84 (m, 1H, H-3'), 6.55 (bs, 2H, NH_2), 7.35 (m, 15H, Ph x 3), 7.68 (s, 1H, H-8), 12.5 (bs, 1H, NH); MS *m/z* 554 $(M + H)^+$.

(2S,3R)-3-(6-Chloro-9H-purin-9-yl)-1,2,6-trihydroxyhexane **5a** :

Boron tribromide (1.1 mL, 1M in dichloromethane) was added dropwise at -78°C to a solution of **18a** (183 mg, 0.33 mmol) in 15 mL of anhydrous dichloromethane. After stirring for 1 h at -78°C, 4 mL of a saturated solution of $NaHCO_3$ were added while the

mixture was allowed to warm to room temperature. The organic layer was washed with water (3 x 5 mL) and the aqueous phases were pooled to be concentrated to dryness. The residue was taken up in tetrahydrofuran (2 x 4 mL) and after filtrating, concentration to dryness and purification by column chromatography (acetonitrile - methanol, 9 : 1, Rf 0.24) give **5a** (84 mg, 88 %); $[\alpha]_D$ + 13° (*c* 0.9 MeOH); UV (EtOH, 95%) λ_{max} 265 (ε 8525) nm; IR (KBr) ν_{max} 3375 (OH), 2930, 2890 (CH), 1595, 1560 (C=C, C=N) cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O, 250 MHz) δ 1.00-1.21 (m, 2H, CH_2-5'), 1.91 and 2.05 (2m, 2H, CH_2-4'), 3.16 (m, 2H, CH_2-1'), 3.27 (t, 2H, J = 6.5 Hz, CH_2-6'), 3.90 (dd, 1H, J = 5, 10 Hz, H-2'), 4.70 (m, 1H, H-3'), 8.64 and 8.73 (2s, 1H x 2, H-2 and H-8); MS *m/z* 287 and 289 $(M + H)^+$.

(2S,3R)-3-(2-Amino-6-chloro-9H-purin-9-yl)-1,2,6-trihydroxyhexane **5b** :

Procedure as per compound **5a**. Compound **18b** (240 mg, 0.42 mmol) and BBr_3 (1.6 mL, 1 M) in CH_2Cl_2 (18 mL) gave, after hydrolysis ($NaHCO_3$, 5mL) and extraction, a residue which was taken up in tetrahydrofuran-methanol, 9 : 1 (3 mL x 2) then chroma - tographed (acetonitrile-methanol, 85:15, Rf 0.38) to give **5b** (87 mg, 69 %); $[\alpha]_D$ +14° (*c* 0.7 MeOH); UV (EtOH, 95%) λ_{max} 224 (ε 23310), sh 250 (5260), 312 (6070) nm; IR (KBr) ν_{max} 3390 (OH), 2935, 2890 (CH), 1615, 1570 (C=C, C=N) cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O, 250 MHz) δ 1.04-1.22 (m, 2H, CH_2-5'), 1.84 and 1.96 (2m, 2H, CH_2-4'), 3.14 (m, 2H, CH_2-1'), 3.27 (t, 2H, J = 6 Hz, CH_2-6'), 3.83 (dd, 1H, J = 5, 10 Hz, H-2'), 4.42 (m, 1H, H-3'), 6.81 (s, 2H, NH_2), 8.06 (s, 1H, H-8); MS *m/z* 302 and 304 $(M + H)^+$, 268 $(M + 2H - Cl)^+$.

9-[(2S,3R)-1,2,6-Trihydroxyhex-3-yl]-hypoxanthine **6a** :

Procedure as per compound **5a**. Compound **19a** (107 mg, 0.20 mmol) and BBr_3 (775 mL, 1 M) in CH_2Cl_2 (10 mL) gave after hydrolysis ($NaHCO_3$, 2 mL) and extraction a residue which was chromatographed (acetonitrile-methanol, 8:2, Rf 0.12) to give **6a** (32 mg, 60 %); mp 212°C; $[\alpha]_D$ + 17.5° (*c*1.3 MeOH); UV (EtOH, 95%) λ_{max} 250 (ε 10960) nm; IR (KBr) ν_{max} 3408 (OH), 2960, 2880 (CH), 1693 (C=O), 1595 (C=C, C=N) cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O, 250 MHz) δ 1.04-1.22 (m, 2H, CH_2-5'), 1.87 and 1.96 (2m, 2H, CH_2-4'), 3.12 (m, 2H, CH_2-1'), 3.26 (t, 2H, J = 6 Hz, CH_2-6'), 3.82 (dd, 1H, J = 5, 10 Hz, H-2'), 4.52 (m, 1H, H-3'), 7.97 and 8.00 (2s, 1H x 2, H-2 and H-8); MS *m/z* 269 $(M + H)^+$; HRMS calc. for $C_{11}H_{16}N_4O_4$ 268.1171, found 268.1174.

9-[(2S,3R)-1,2,6-Trihydroxyhex-3-yl]-guanine **6b** :

Procedure as per compound **5a** .Compound **19b** (70 mg, 0.13 mmol) and BBr_3 (500 mL, 1 M) in CH_2Cl_2 (8 mL) gave after hydrolysis ($NaHCO_3$, 1.5mL) and extraction a residue which was purified by column chromatography (acetonitrile-methanolic ammonia, 7:3, Rf 0.15) to give **6b** (28 mg, 77 %). Mp : 158°C (decomp.); $[\alpha]_D$ + 24°

(*c*1.2 MeOH); UV (EtOH, 95%) λ_{max} 254 (ε 12530), sh 272 (8350) nm; IR (KBr) ν_{max} 3350, 3140 (OH, NH_2), 2935 (CH), 1690 (C=O), 1610, 1535 (C=C, C=N) cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O, 250 MHz) δ 1.08-1.23 (m, 2H, CH_2-5'), 1.82 (m, 2H, CH_2-4') , 3.07 (m, 2H, CH_2-1'), 3.27 (t, 2H, J = 6 Hz, CH_2-6'), 3.73 (m, 1H, H-2'), 4.31 (m, 1H, H-3'), 6.49 (s, 2H, NH_2) 7.56 (s, 1H, H-8), 10.70 (bs, 1H, NH); MS *m/z* 284 $(M + H)^+$; HRMS calc. for $C_{11}H_{17}N_5O_4$ 283.1280, found 283.1283.

9-[(2S,3R)-1,2,6-Trihydroxyhex-3-yl]-adenine **7a** :

A solution of **5a** (31 mg, 0.11 mmol) in saturated methanolic ammonia (5 mL) was heated in a stainless steel bomb at 90°C for 5 h. Ammonia and methanol were evaporated. The residue was purified by column chromatography (acetonitrile-methanol, 8:2) to afford adenine derivative **7a** (22 mg, 75 %); $[\alpha]_D$ + 20° (*c*1.1 MeOH); UV (EtOH, 95%) λ_{max} 261 (ε 14760) nm; IR (KBr) ν_{max} 3380 (NH_2, OH), 2935, 2880 (CH), 1650, 1600 (C=C, C=N) cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O, 250 MHz) : δ 1.10-1.30 (m, 2H, CH_2-5'), 1.91 and 2.06 (2m, 2H, CH_2-4'), 3.14 (d, 2H, J = 5 Hz, CH_2-1'), 3.33 (t, 2H, J = 6.5 Hz, CH_2-6'), 3.89 (dd, 1H, J = 5, 10 Hz, H-2'), 4.58 (m, 1H, H-3'), 7.20 (s, 2H, NH_2), 8.09 and 8.12 (2s, 1H x 2, H-2 and H-8); MS *m/z* 268 $(M + H)^+$; HRMS calc. for $C_{11}H_{17}N_5O_3$ 267.1331, found 267.1331.

6-Amino-9-[(2S,3R)-1,2,6-trihydroxyhex-3-yl]-adenine **7b** :

Compound **5b** reacted with ammonia as described above. Purification by column chromatography (acetonitrile-methanol, 8:2) afforded **7b** (26 mg, 40 %); $[\alpha]_D$ + 28° (*c*1.5 MeOH); UV (EtOH, 95%) λ_{max} 216 (ε 24670), 255 (7660), 281 (9250) nm; IR (KBr) ν_{max} 3435 (NH_2, OH), 2930, 2890 (CH), 1625, 1600 (C=C, C=N) cm^{-1}; ^1H NMR (DMSO-d_6 + D_2O, 250 MHz) δ 1.10-1.27 (m, 2H, CH_2-5'), 1.79 and 1.92 (2m, 2H, CH_2-4'), 2.95 (m, 2H, CH_2-1'), 3.12 (t, 2H, J = 6 Hz, CH_2-6'), 3.74 (m, 1H, H-2'), 4.33 (m, 1H, H-3'), 5.78 (s, 2H, NH_2), 6.65 (s, 2H, NH_2), 7.60 (s, 1H, H-8); MS *m/z* 283 $(M + H)^+$; HRMS calc. for $C_{11}H_{18}N_6O_3$ 282.1440, found 282.1443.

Acknowledgements : the authors would like to thank Dr M.Legraverend (Institut Curie, Orsay) for a generous gift of compounds **16b**, Ms G.Flad for running the spectral determinations. This work was supported by a grant from the Agence Nationale de la Recherche contre le Sida.

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Received 10/12/92
Accepted 4/2/93