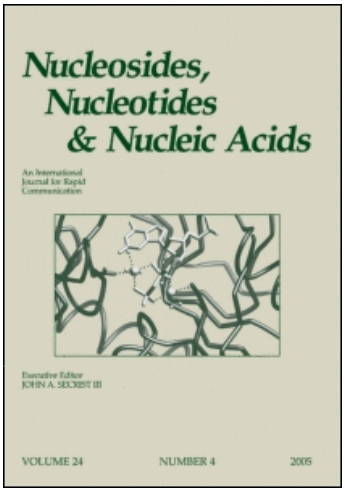

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Synthesis of Some Purine Carbocyclic Isosteres of 2',3'-Dideoxy-3'-C-Hydroxymethyl Nucleosides as Potential Inhibitors of HIV

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SYNTHESIS OF SOME PURINE CARBOCYCLIC ISOSTERES OF 2',3'-DIDEOXY-3'-*C*-HYDROXYMETHYL NUCLEOSIDES AS POTENTIAL INHIBITORS OF HIV

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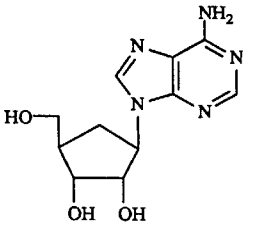
Abstract

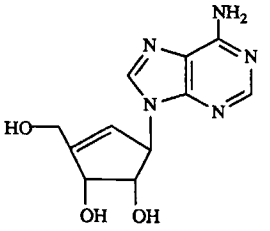
The synthesis of some enantiomerically pure carbocyclic 2',3'-dideoxy-3'-*C*-hydroxymethyl derivatives of adenine, inosine and guanine is described. The Mitsunobu reaction was used in the coupling procedure giving exclusively N^9-coupling.The nucleosides were tested for inhibition of HIV multiplication *in vitro* and were found to be inactive in the assay.

Introduction

The design and synthesis of potent and selective antiviral agents is one of the major goals for medicinal chemists in the antiviral field, and in recent years several new types of nucleoside analogues have been identified as selective antiviral agents. In particular carbocyclic nucleosides, which have the furanose ring oxygen replaced by a methylene group, have emerged as particularly interesting.[1]

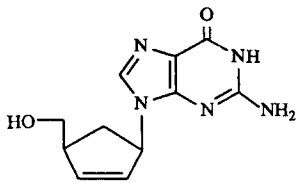


1



2

The carbocyclic adenosine analogues (-)-aristeromycin[2] **1** and (-)-neplanocin A[3] **2** as well as the corresponding analogues lacking the hydroxymethyl substituent of the cyclopentane ring have been shown to be active against a broad range of (-) RNA and (±) RNA viruses [but not (+) RNA viruses (i.e. retroviruses)].[4,5] The mode of antiviral effect for these compounds has been attributed to the inhibition of the cellular enzyme *S*-adenosylhomocysteine (AdoHcy) hydrolase which decreases viral 5'-cap mRNA methylation.[6] The carbocyclic 2',3'-didehydro-2',3'-dideoxyguanosine (carbovir) **3** is active against HIV[7] and carbocyclic oxetanocin analogues such as cyclobut-A **4** and cyclobut-G **5** are active against both HIV and herpesviruses.[8,9] Carbocyclic 2'-deoxyguanosine **6** and carbocyclic 2'-ara-fluoroguanine derivative **7** have both shown potent activity against HSV-1 and HSV-2 *in vitro*.[10,11]



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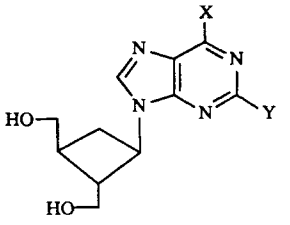
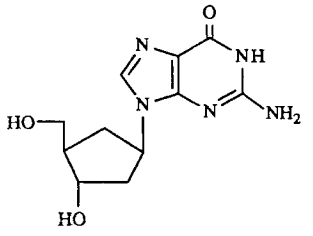


4: X=NH_2, Y=H
5: X=OH, Y=NH_2



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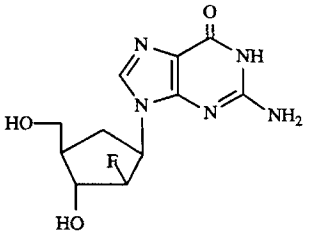


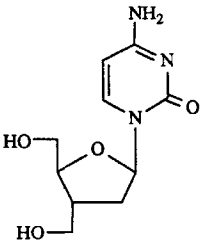
7

The carbocyclic nucleoside family can chemically be viewed as cyclopentane substituted purines or pyrimidines. The conventional glycosidic linkage is thus lacking for these compounds which advantageously makes them more stable to enzymatic and acid hydrolysis.[12,13] Also the substitution of oxygen by a methylene group results in a comparatively higher lipophilicity which could have a positive effect on passive absorption and thus bioavailability.

Chirality is known to play a critical role in biological systems and not surprisingly this has also held true for the antiviral activity of nucleoside derivatives

including carbocyclic nucleoside analogues. In general and as far as is known regarding racemic mixtures, the enantiomer corresponding to the naturally derived nucleoside has by far the highest antiviral activity i.e. 3'-azido-3'-deoxythymidine (AZT, Zidovudine®),[14] carbovir,[15] 2',3'-dideoxy-3'-*C*-hydroxymethylcytidine,[16] cyclobut-A and cyclobut-G,[17] carba-5-iodo-2'-deoxyuridine and carba-(E)-5-(2-bromovinyl)-2'-deoxyuridine.[18]

In carbocyclic nucleosides it has mainly been the purine analogues which have shown anti-HIV activity. We have previously shown that 2',3'-dideoxy-3'-*C*-hydroxymethylcytidine **8** has potent anti-HIV activity in vitro.[19]



8

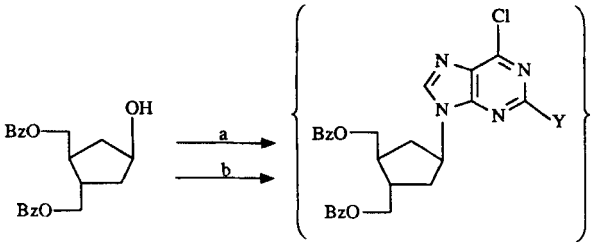
As the corresponding carbocyclic nucleosides in the purine series have not been synthesized we decided to prepare the corresponding adenosine, inosine and guanine carbocycles (**12**, **13**, **14**) in the stereochemically pure form, as well as their corresponding enantiomers. After this work was completed the preparation of racemic forms of **12** and **14** was reported.[20]

Results and Discussion

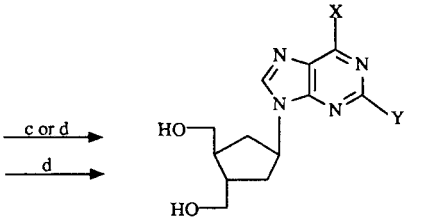
We have recently developed stereospecific synthesis of both cyclopentanol enantiomers **9** and **15**[21] which were used as starting materials in this synthesis. The secondary hydroxyl group in cyclopentanol derivative **9** was substituted with 6-chloropurine and 2-amino-6-chloropurine respectively using the Mitsunobu procedure (triphenylphosphine-diethyl azodicarboxylate)[22] to give compounds **10** and **11**. Due to the C_2 symmetry of **9** and **15** only one stereoisomer is obtained as product in the reaction. The Mitsunobu procedure is known to preferentially give the N^9-substituted product[23] whereas many of the other direct coupling methods of purines and especially 2,6-disubstituted purines also give substantial amounts of the corresponding N^7-isomer.[24]

The crude 6-chloropurine derivative **10** was reacted with methanolic ammonia to give the corresponding deprotected carbocyclic adenosine derivative **12** in 52%

Scheme I[a]



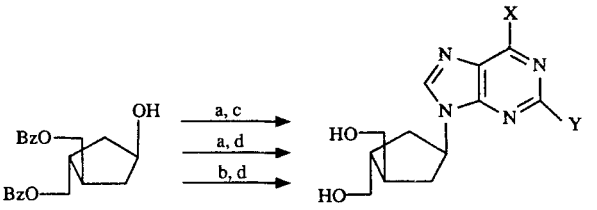
9 **10:** Y = H
11: Y = NH_2



12: X = NH_2, Y = H (52%)
13: X = OH, Y = H (40%)
14: X = OH, Y = NH_2 (40%)

[a](a) 6-chloropurine, Ph_3P-DEAD, THF; (b) 2-amino-6-chloropurine, Ph_3P-DEAD, THF; (c) NH_3, MeOH, 80°C; (d) aqueous NaOH, 100°C.

Scheme II[a]



15

16: X = NH_2, Y = H (48%)
17: X = OH, Y = H (40%)
18: X = OH, Y = NH_2 (40%)

[a](a) 6-chloropurine, Ph_3P-DEAD, THF; (b) 2-amino-6-chloropurine, Ph_3P-DEAD, THF; (c) NH_3, MeOH, 80°C; (d) aqueous NaOH, 100°C.

overall yield, or was reacted with aqueous sodium hydroxide to give the corresponding deprotected carbocyclic inosine derivative **13** in 40% overall yield. The crude 2-amino-6-chloropurine derivative **11** was reacted with aqueous sodium hydroxide to give the corresponding deprotected carbocyclic guanosine **14** in 40% overall yield. The N^7-isomers were not found in detectable amounts in the isolated products. The N^7-, N^9-regioselectivity of the alkylations was asserted by UV[25] and NMR spectroscopy.[26]

The enantiomers **16**, **17** and **18** corresponding to **12**, **13** and **14** were obtained using the same synthetic protocol (*vide supra*) but starting from **15** in place of **9**.

Compounds **12-14** and **16-18** were tested for inhibition of HIV multiplication in a XTT assay on M4 cells[27] and were all found to be inactive.

Experimental Section

TLC was performed on Merck precoated 60 F-254 plates. Spots were visualized by UV-light and/or charring with ethanolic sulfuric acid. Column chromatoghraphy was performed using silica gel 60 (0.040-0.063 mm, Merck). HPLC was performed on a prepacked steel column (250 x 25 mm) using Polygosil 60-7, C-18 (Macherey-Nagel). NMR spectra were recorded with a Bruker AC 250 instrument, using DMSO-d_6 solutions. TMS was used as internal standard. The shifts were reported in ppm (δ scale). UV absorption spectra were recorded with a Perkin-Elmer Lambda 5 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

(3S,4S)-6-Amino-9-[3,4-bis(hydroxymethyl)cyclopentyl]-9*H*-purine (12).

To a suspension of triphenylphosphine (178 mg, 0.68 mmol) and 6-chloropurine (105 mg, 0.68 mmol) in tetrahydrofuran (2 mL) under a nitrogen atmosphere was added diethylazodicarboxylate (0.12 mL, 0.80 mmol), and the resulting yellow solution was stirred for 5 min at room temperature. A solution of (3S,4S)-3,4-bis(benzoyloxymethyl)cyclopentanol **9** (135 mg, 0.38 mmol) in tetrahydrofuran (1 mL) was added, and the mixture was stirred for 18 h. The solvent was evaporated and the residue was purified by flash column chromatography (toluene-ethyl acetate, 2:1). The crude compound was treated with methanolic ammonia (5 mL, saturated) in a sealed reaction vessel at 80°C. After 18 h the solvent was removed and the residue was purified by column chromatography (chloroform-methanol, 9:1) to give compound **12** as a syrup (52 mg, 52%). A small amount was purified by HPLC (water-methanol, 80:20, v/v) to give an analytical sample, which was recrystallized from ethanol: mp 168-169°C; $[\alpha]^{20}_D$ +16.8° (*c* 1.04, H_2O); UV (H_2O) λ_{max} 260.2 nm (ε 13 820); ^{1}H NMR (250.13

MHz) δ 1.90 - 2.34 (m, H-2', H-3', H-4', H-5'), 3.36 - 3.56 (m, 2 CH_2O), 4.51 (br s, 2 O*H*), 4.80 - 4.86 (m, H-1'), 6.90 (s, NH_2), 8.13, 8.17 (2 s, H-2, H-8); ^{13}C NMR (62.90 MHz) δ 34.6, 35.9, 42.1, 43.1 (C-2', C-3', C-4', C-5'), 53.7 (C-1'), 64.0, 64.1 (2 *C*H_2O), 119.2 (C-5), 138.9 (C-8), 149.4 (C-4), 151.9 (C-2), 155.8 (C-6). Anal. Calcd for $C_{12}H_{17}O_2N_5 \cdot 0.25\ H_2O$: C, 53.8; H, 6.6; N, 26.1. Found: C, 53.8; H, 6.6; N, 26.0.

(3R,4R)-6-Amino-9-[3,4-bis(hydroxymethyl)cyclopentyl]-9*H*-purine (16).

Compound **16** was prepared from (3R,4R)-3,4-bis(benzoyloxymethyl)cyclopentanol **15**, in the same manner as described for compound **12**, to give the title compound **16** in a yield of 48%. **16**: $[\alpha]^{20}_D$ -16.5° (*c* 1.1, H_2O); UV (H_2O) λ_{max} 260.2 nm (ε 14 271). Anal. Calcd for $C_{12}H_{17}O_2N_5 \cdot 0.25\ H_2O$: C, 53.8; H, 6.6; N, 26.1. Found: C, 53.6; H, 6.6; N, 26.0.

(3S,4S)-9-[3,4-bis(hydroxymethyl)cyclopentyl]-1,9-dihydro-purin-6(6*H*)-one (13).

To a suspension of triphenylphosphine (113 mg, 0.43 mmol) and 6-chloropurine (66 mg, 0.43 mmol) in tetrahydrofuran (3 mL) under a nitrogen atmosphere was added diethylazodicarboxylate (0.08 mL, 0.51 mmol) and the resulting yellow solution was stirred for 5 min at room temperature. A solution of (3S,4S)-bis(benzoyloxymethyl)-cyclopentanol **9** (85 mg, 0.24 mmol) was added and the mixture was stirred for 18 h. The solvent was evaporated and the residue was purified by flash column chromatography (toluene-ethyl acetate, 2:1). The crude compound was dissolved in aqueous sodium hydroxide (2 mL, 1 M) and refluxed for 4 h. After cooling to room temperature the mixture was neutralized with aqueous hydrogen chloride (2 M), and concentrated to a small volume, which was applied to a column containing 160 mL of Sephadex LH-20. The column was eluted with water and the product containing fractions were combined, concentrated to a small volume and purified by HPLC (water-mathanol, 85:15, v/v) to give compound **13** (25.6 mg, 40%), which was recrystallized from ethanol: mp 83-84°C; $[\alpha]^{20}_D$ +18.7° (*c* 1.01, H_2O); UV (H_2O) λ_{max} 249.5 nm (ε 12 052); ^{1}H NMR (250.13 MHz) δ 1.82 - 2.34 (m, H-2', H-3', H-4', H-5'), 3.35 - 3.55 (m, 2 CH_2O), 4.78 - 4.85 (m, H-1'), 7.96, 8.11 (2 s, H-2, H-8); ^{13}C NMR (62.90 MHz) δ 35.1, 36.4, 42.3, 43.2 (C-2', C-3', C-4', C-5'), 54.3 (C-1'), 64.1, 64.2 (2 *C*H_2O), 124.5 (C-5), 138.3 (C-8), 145.0 (C-2), 148.4 (C-4), 156.7 (C-6). Anal. Calcd for $C_{12}H_{16}O_3N_4 \cdot 0.3\ H_2O$: C, 53.4; H, 6.2; N, 20.8. Found: C, 53.4; H, 6.6; N, 20.7.

(3R,4R)-9-[3,4-bis(hydroxymethyl)cyclopentyl]-1,9-dihydro-purin-6(6*H*)-one (17).

Compound **17** was prepared from (3R,4R)-3,4-bis(benzoyloxymethyl)cyclopentanol **15**, in the same manner as described for compound **13**, to give the title

compound **17** in a yield of 40%. **17**: $[\alpha]^{20}_D$ -17.0° (*c* 1.0, H_2O); UV (H_2O) λ_{max} 250.0 nm (ϵ 11 444). Anal. Calcd for $C_{12}H_{16}O_3N_4 \cdot 0.3H_2O$: C, 53.4; H, 6.2; N, 20.8. Found: C, 53.3; H, 6.8; N, 20.7.

(3S,4S)-2-Amino-9-[3,4-bis(benzoyloxymethyl)cyclopentyl]-1,9-dihydro-purin-6(6*H*)-one (14).

To a suspension of triphenylphosphine (334 mg, 1.28 mmol) and 2-amino-6-chloropurine (215 mg, 1.27 mmol) in tetrahydrofuran (10 mL) under a nitrogen atmosphere was added diethylazodicarboxylate (0.22 mL, 1.40 mmol) and the resulting yellow mixture was stirred for 5 min at room temperature. A solution of (3S,4S)-bis(benzoyloxymethyl)cyclopentanol **9** (133 mg, 0.38 mmol) in tetrahydrofuran (2 mL) was added and the mixture was stirred for 18 h. The solvent was evaporated and the residue was purified by flash column chromatography (toluene-ethyl acetate, 2:1). The crude compound was suspended in aqueous sodium hydroxide (3 mL, 1 M), and refluxed. After 4 h the solution was allowed to cool to room temperature and neutralized with aqueous hydrogen chloride (2 M). The mixture was concentrated to a small volume, and applied to a column containing 160 mL of Sephadex LH-20. The column was eluted with water, and the product containing fractions were combined, concentrated to a small volume and purified by HPLC (water-methanol, 80:20, v/v) to give compound **14** (42 mg, 40%), which was recrystallized from water: mp 276-277°C; $[\alpha]^{20}_D$ +28.1° (*c* 0.096, H_2O); UV (H_2O) λ_{max} 253 nm (ϵ 10 039), shoulder 275 nm (ϵ 7 070); ^{1}H NMR (250.13 MHz) δ 1.70 - 2.29 (m, H-2', H-3', H-4', H-5'), 3.32 - 3.54 (m, 2 C*H*$_2$O, O*H*), 4.22 - 4.68 (m, H-1', O*H*), 6.26 (br s, N*H*$_2$), 7.74 (s, H-8); ^{13}C NMR (62.90 MHz) δ 34.7, 36.2, 42.0, 43.0 (C-2', C-3', C-4', C-5'), 53.0 (C-1'), 64.0, 64.1 (2 *C*H$_2$O), 116.8 (C-5), 134.9 (C-8), 150.9 (C-4), 153.1 (C-2), 156.6 (C-6). Anal. Calcd for $C_{12}H_{17}O_3N_5 \cdot 1.25\ H_2O$: C, 47.8; H, 6.5; N, 23.2. Found: C, 47.4; H, 6.4; N, 23.4.

(3R,4R)-2-Amino-9-[3,4-bis(hydroxymethyl)cyclopentyl]-1,9-dihydro-purin-6(6*H*)-one (18).

Compound **18** was prepared from (3R,4R)-bis(benzoyloxymethyl)cyclopentanol **15**, in the same manner as described for compound **14**, to give the title compound **18** in a yield of 40%. **18**: $[\alpha]^{20}_D$ -27.1° (*c* 0.096, H_2O); UV (H_2O) λ_{max} 252.5 nm (ϵ 13 801), shoulder 275 nm (ϵ 10 780). Anal. Calcd for $C_{12}H_{17}O_3N_5 \cdot 1.75\ H_2O$: C, 46.4; H, 6.6; N, 22.5. Found: C, 46.3; H, 6.2; N, 22.6.

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