Pergamon

Tetrahedron 54 (1998) 2833–2842

TETRAHEDRON

Synthesis of Novel Carbocyclic Nucleosides with a Cyclopentenyl Ring: Homocarbovir and Analogues

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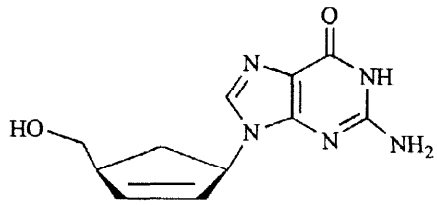
Received 7 October 1997; accepted 15 January 1998

Abstract: Several synthetic strategies have been used to prepare (±)-*cis*-4-(aminomethyl)-2-cyclopentenylmethanol (**6**) from norbornadiene. Amino alchohol **6** has been then used to prepare an homologue of carbovir and its congeners. Alternatively, a synthetic intermediate in the preparation of **6** can be used in a convergent mode to prepare the corresponding adenine and inosine analogues.

Carbocyclic analogues of nucleosides (CANs) have recently become the object of increased interest owing to their proven antineoplastic[1] and antiviral[2] properties. Among the antiviral CANs discovered in the search for agents active against human immunodeficiency virus and hepatitis B virus, one of the most promising is carbovir (**1**), which inhibits reverse transcriptase *in vitro*.[3,4]



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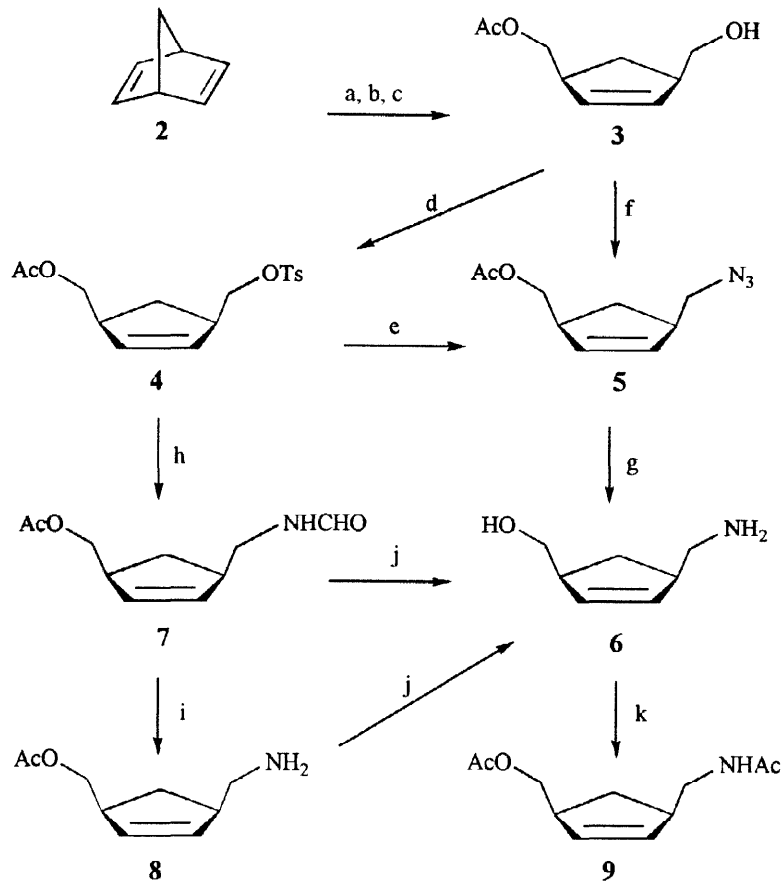
The work reported here describes the synthesis of the carbovir homologue **14**, its congener with an adenine base, **16**, and the related analogues **15** and **17**, all of which contain a methylene group between the pseudosugar and the purine base. Our interest in these compounds lies in the increased flexibility this extra methylene confers upon them, and its implications for their biological properties.

The CANs were prepared starting from the amino alcohol precursor, **6**. With a view to improving the existing route to **6**,[5] we explored various alternative approaches starting from norbornadiene (**2**) and going via the monoacetate **3** (Scheme 1). Although these approaches used racemic intermediates, they are equally applicable to homochiral intermediates, which can be obtained by preparing (1*R*,1*S*)-**3** by the published enzymatic procedure.[6]

0040-4020/98/$19.00
PII: S0040-4020(98)00037-4



Reaction conditions:
a) O_3 (-78°C); b) $NaBH_4$; c) Ac_2O/Pyr; d) TsCl/Pyr; e)NaN_3/Aliquat;
f) $Zn(N_3)_2(C_5H_5N)_2/Ph_3P$/DEAD; g) $LiAlH_4$; h) $NaN(CHO)_2$/DMF, then H_2O;
i) HCl/EtOH-H_2O, r.t.; j) 2N HCl, reflux; k)Ac_2O/Pyr

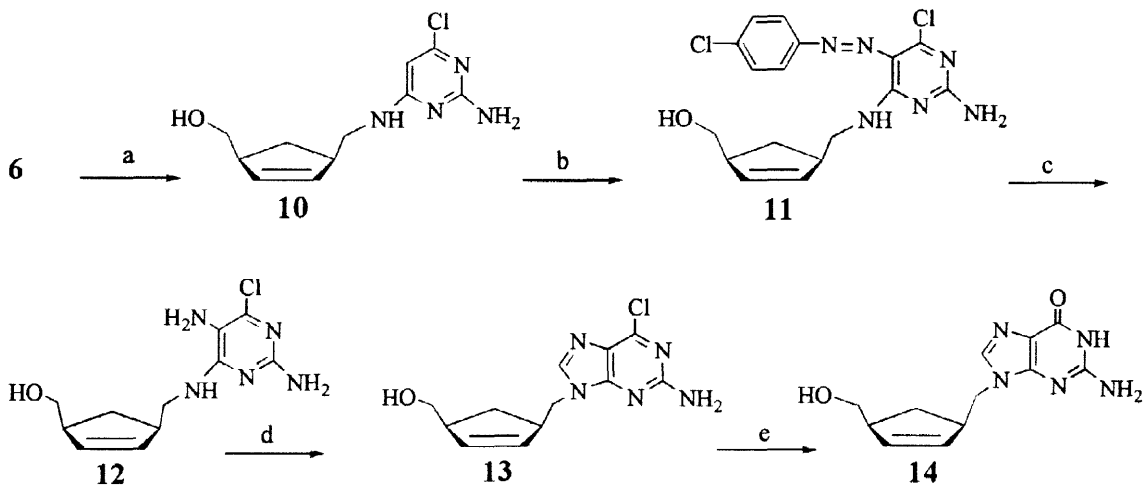
Scheme 1

Azide intermediate **5** was firstly prepared by conversion of compound **3**[5] to tosylate **4** by room-temperature reaction with tosyl chloride in dry pyridine (63% yield),[5] followed by nucleophilic displacement of the tosylate by sodium azide in a heterogeneous system containing methyltrioctylammonium chloride (Aliquat 336) as phase transfer catalyst. Although the latter reaction gave azide **5** in a respectable 85% yield, the rather a modest yield of the first step led us to explore the possibility of obtaining azide **5** directly from monoacetate **3**, by Mitsunobu reaction with the bis-pyridine complex of zinc azide $[Zn(N_3)_2(C_5H_5N)_2]$.[7] Gratifyingly, this gave azide **5** in 77% yield from **3**.

Reduction of azide **5** with lithium aluminium hydride in tetrahydrofuran gave amino alcohol **6** in only 46% yield, which was attributed to the ability of the amino alcohols to act as bidentate ligands in complexes with the aluminium cation, which made them difficult to isolate. Addition of triethanolamine in the hydrolysis step did not appreciably improve the yield of **6**.[8] To circumvent this problem, we sought an alternative approach

to **6**, in the first instance applying a modified Gabriel synthesis to **4**, using sodium diformylamide as the nitrogen source instead of potassium phthalimide.[9] Thus, treatment of **4** with $NaN(CHO)_2$ in dry dimethylformamide gave a 79% yield of formamide **7**, the diformyl imide product presumably having undergone partial hydrolysis during work-up. Acid hydrolysis of **7** in aqueous ethanol at room temperature gave a quantitative yield of amino ester **8**, it being necessary to treat **8** (or **7**) with 2N HCl at reflux for 5 h in order to obtain the desired amino alcohol **6** (83% yield). Microanalysis and spectroscopic characterization of amino alcohol **6** were supported by characterization of its diacetyl derivative **9**.

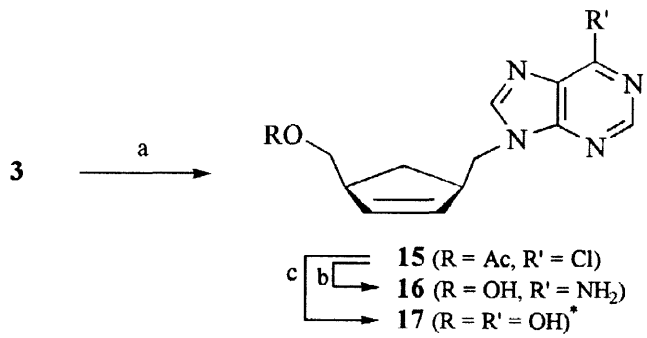
Homocarbovir **14** was prepared by the general synthetic approach to carbocyclic guanine nucleosides (Scheme 2).[10,11] Firstly, amino alcohol **6** was condensed with 2-amino-4,6-dichloropyrimidine, affording diamine **10**. Then **10** was coupled with 4-chlorobenzenediazonium chloride, and the resulting 5-(4-chlorophenylazo)pyrimidine **11** was reduced to triaminopyrimidine **12** with zinc in acetic acid. Cyclization of **12** with triethyl orthoformate gave chloropurine **13**, which was converted into **14** by refluxing it in aqueous sodium hydroxide.



Reaction conditions:
a) 2-Amino-4,6-dichloropyrimidine; b) $4\text{-}ClC_6H_4N_2^+Cl^-$;c) Zn/AcOH; d) $HC(OEt)_3/H^+$ e) NaOH, Δ

Scheme 2

The adenine and other carbonucleosides were prepared by a convergent approach starting with the Mitsunobu reaction of **3** with 6-chloropurine (Scheme 3).[12] The resulting 6-chlorinated purine carbonucleoside, **15** (36% yield), was then treated with ammonia or sodium hydroxide, affording adenosine analogue **16** and inosine analogue **17**, respectively. Although the yield of **15** was rather low, this approach has the advantage that it has fewer steps than alternative approaches such as that used to prepare **14**.



Reaction conditions: a) 6-Chloropurine /Ph_3P/DEAD; b) NH_3; c) NaOH

Sheme 3

EXPERIMENTAL PART

Melting points are uncorrected and were determined on a Reichert Kofler Thermopan. IR spectra of samples as KBr discs (for solids) or films between NaCl plates (for oils) were recorded in a Perkin Elmer FTIR 1640 spectrometer. ^1H and ^{13}C NMR spectra were recorded in a Bruker AMX-300 spectrometer, at 300 and 75 MHz, respectively, with TMS as internal standard. MS spectra were recorded on Kratos MS-50 apparatus. Microanalyses were done at the Microanalysis Service, University of Santiago, using a Perkin-Elmer 240B Elemental Analyser. Silica gel (400 mesh) for flash chromatography (FC) was from Merck. Reagents and solvents were of commercial grade and were supplied by Aldrich Chemical Co. *cis*-4-(Hydroxymethyl)-2-cyclopentenylmethyl acetate (**3**) and *cis*-4-(tosyloxymethyl)-2-cyclopentenylmethyl acetate (**4**) were prepared from norbornadiene by published methods.[5]

***cis*-4-(Azidomethyl)-2-cyclopentenylmethyl acetate (5)** *Method A.* Compound **4** (2.5 g, 7.7 mmol) was stirred into a solution of sodium azide (1g, 15.5 mmol) and Aliquat 336 (0.3 g, 0.75 mmol) in water (5 mL), and then heated at 75°C for 4h. The mixture was allowed to cool and was then extracted with ethyl acetate, and the organic layer was separated, washed with saturated brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave 1.75 g of an oil, which was chromatographed using toluene as eluent, giving **5** (1.27 g, 85%) as a spectroscopically pure (^1H NMR), colourless oil.

Method B. A 1M aqueous solution of sodium azide (10 mL) was poured into a 1M solution of zinc nitrate (10 mL). The suspended precipitate formed was warmed and treated dropwise with pyridine until it dissolved. Upon cooling this solution, colourless needle-shaped crystals of the bis-pyridine complex $[Zn(N_3)_2(C_5H_5N)_2]$ formed,[14] which were suction-filtered out and dried under vacuum at room temperature until they had constant mass. The dried Zn complex (1.29 g, 4.2 mmol, 8.4 equiv.) was added to a stirred solution of monoacetate **3**

(1 g, 6 mmol) and triphenylphosphine (3.15 g, 12 mmol) in dry toluene (24 mL), followed dropwise by diethyl azodicarboxylate (12 mL). The disappearance of **3** was monitored by tlc, and when this was complete the solvent was evaporated and the crude product was flash-chromatographed using toluene as eluent. Compound **5** (0.88 g, 77%) was isolated as a colourless oil. IR (ν): 2956, 2097, 1741, 1450, 1385, 1364, 1244, 1037; ^{1}H NMR ($CDCl_3$), δ: 1.27 (1H; dt, J_d = 13.42, J_t = 6.65, 5-HH), 2.06 (3H, s, CH_3), 2.28 (1H, dt, J_d = 13.42, J_t = 8.63, 5-HH), 2.99 (1H, dq, J_d =8.64, J_q = 6.62, 4-H), 3.04 (1H, dq, J_d = 8.63, J_q = 6.54, 1-H), 3.28 (2H, d, J = 6.62, 4-CH_2), 4.00 (1H, part A of a ABM system, J_{AB} = 10.76, J_{AM} = 6.59, 1-CHH), 4.05 (1H, part B of a ABM system, J_{BA} = 10.76, J_{BM} = 6.58, 1-CHH), 5.75 (2H, s, 2-H + 3-H). ^{13}C NMR ($CDCl_3$), δ: 171.54, 133.75, 133.67, 68.11, 56.59, 46.25, 45.51, 31.28, 21.36. Anal.Calcd for $C_9H_{13}N_3O_2$: C, 55.37; H, 6.71; N, 21.52. Found: C, 55.10; H, 6.48; N, 21.79.

***cis*-4-(Formylaminomethyl)-2-cyclopentenylmethyl acetate (7)** A mixture of formamide (1.8 g 40 mmol) and freshly prepared sodium methoxide (0.46 g Na in 5 mL MeOH) was stirred at room temperature until the sodium had dissolved (1 h). The solvent was evaporated *in vacuo* and the crystalline solid residue was dried in a vacuum desiccator for 3 h. The sodium diformylamide (3.56 g, 94%) so obtained was used without further purification.

A mixture of **4** (1 g, 3.08 mmol) and sodium diformylamide (0.34 g, 3.6 mmol) in dry dimethylformamide (2 mL) was stirred at 100°C for 3 h. The mixture was cooled and the solvent was evaporated *in vacuo*. The solid was triturated in ethyl acetate (3 x 5 mL), and the extracts were filtered, combined, washed with water (2 x 5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* gave a crude product, which was flash-chromatographed using 1:1 dichloromethane/ethyl acetate as eluent. Compound **7** (0.33 g, 79%) was isolated as slightly yellow oil. IR (ν): 3297, 3052, 2953, 1738, 1537, 1385, 1245. ^{1}H NMR ($CDCl_3$), δ: 1.21 (1H, dt, J_d = 13.38, J_t = 6.73, 5-HH), 2.06 (3H, s, CH_3), 2.25 (1H, dt, J_d = 13.38, J_t = 8.71, 5-HH), 2.97-3.08 (2H, m, 1-H + 4-H), 3.27 (1H, dt, J_d = 13.45, J_t = 5.95, 4-CHH), 3.41 (1H, dt, J_d = 13.45, J_t = 6.45, 4-CHH), 3.99 (1H, part A of a ABM system, J_{AB} = 10.71, J_{AM} = 6.20, 1-CHH), 4.05 (1H, part B of a ABM system, J_{BA} = 10.71, J_{BM} = 6.63, 1-CHH), 5.69 (1H, bs, NH), 5.69-5.77 (2H, m, 2-H + 3-H), 8.20 (1H, s, CHO). ^{13}C NMR ($CDCl_3$), δ: 171.71, 162.26, 133.95, 133.60, 68.14, 67.87, 45.51, 42.95, 30.92, 21.46. HRMS *m/z*: Calcd for $C_{10}H_{15}NO_3$: 197.1052. Found: 197.1061.

***cis*-4-(Aminomethyl)-2-cyclopentenylmethyl acetate (8)** A mixture of **7** (0.2 g, 1.01 mmol) and freshly prepared 6% ethanolic HCl (2.5 mL) was stirred at room temperature for 10 days.[10] The solvent and excess HCl were evaporated under reduced pressure, and the crude product was passed through basic ion-exchange resin (Amberlite IRA 420, OH form), using methanol as eluent. Evaporation of the methanol afforded an oil identified as the partial hydrolysis product, **8** (0.17 g, 100%). ^{1}H NMR (Cl_3CD), δ: 1.47 (1H, dt, J_d = 13.61, J_t = 4.82, 5-HH), 2.07 (3H, s, CH_3), 2.29 (1H, dt, J_d = 13.61, J_t = 9.69, 5-HH), 2.67-2.72 (1H, m, 4-H), 2.85-2.98 (3H, m, 1-H + 4-CH_2N), 3.63 (1H, dd, J = 10.58, J = 4.54, 1-CHH), 5.67 (1H, dd, J = 10.58, J = 4.10, 1-

CHH), 5.67 (1H, dt, J_d = 5.66, J_t = 1.94, 3-H), 5.75 (1H, dt, J_d = 5.66, J_t = 1.92, 2-H). ^{13}C NMR ($CDCl_3$), δ: 171.68, 134.57, 133.59, 68.51, 49.08, 46.61, 45.57, 30.72, 21.42. HRMS *m/z*: Calcd for $C_9H_{15}NO_2$: 169.1103. Found: 169.1109.

***cis*-[4-(Aminomethyl)-2-cyclopentenyl]methanol (6)** *Method A.* Lithium aluminium hydride (2.15 g, 56.5 mmol) was carefully added to a cooled (0°C) solution of **5** (1.08 g, 5.52 mmol) in tetrahydrofuran (120 mL). The mixture was stirred and allowed to warm to room temperature and then heated at reflux for 6 h. The reaction was cooled to room temperature and quenched by addition of water-saturated ether followed by water. Then the organic solvents were evaporated *in vacuo* and the aqueous residue was extracted with dichloromethane (3 x 50 mL). The extracts were combined, washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave an oil, which was flash-chromatographed using 1:1 ethyl acetate/methanol as eluent, affording **6** (0.32 g, 46%) as an oily residue.

Method B. A suspension of **8** (0.17 g, 1.01 mmol) in 2 N HCl (10 mL) was heated at reflux for 5 h. The solvent was evaporated *in vacuo* and the solid residue obtained was passed through basic ion-exchange resin (Amberlite IRA 420, OH form), using methanol as eluent. Evaporation of the solvent afforded **6** (0.10 g, 83%) as a colourless oil that darkened upon exposure to air. IR (ν): 3285, 2921, 1734, 1649, 1557, 1334, 1042. ^{1}H NMR ($CDCl_3$), δ: 1.38 (1H, dt, J_d = 13.60, J_t = 5.14, 5-HH), 2.22 (1H, dt, J_d = 13.60, J_t = 9.37, 5-HH), 2.66-2.71 (1H, m, 4-H), 2.77-2.91 (3H, m, 1-H + 4-CH_2), 3.08 (3H, bs, D_2O exch., OH + NH_2,.), 3.68 (1H, part A of a ABM system, J_{AB} = 10.68, J_{AM} = 4.10, 1-CHH), 3.70 (1H, part B of a ABM system, J_{BA} = 10.68, J_{BM} = 4.10, 1-CHH), 5.63 (1H, dt, J_d = 5.69, J_t = 1.96, 3-H), 5.72 (1H, dt, J_d = 5.69, J_t = 1.95, 2-H). ^{13}C NMR ($CDCl_3$), δ: 134.60, 133.84, 66.40, 48.65, 47.71, 46.26, 30.16. EIMS, *m/z* (%): 127 (M^+, 0.92), 79 (100), 77 (53), 67 (52), 66 (58), 65 (45). Anal Calcd for $C_7H_{13}NO$: C, 66.11; H; 10.30; N, 11.01. Found: C, 65.95; H, 10.18; N, 10.92.

***cis*-4-(Acetylaminomethyl)-2-cyclopentenylmethyl acetate (9).** A mixture of **6** (0.2 g, 1.57 mmol) in acetic anhydride and pyridine (2 mL) was stirred at room temperature for 12 h.The solid obtained after concentrations the mixture to dryness was dissolved in CH_2Cl_2 (20 mL), and the organic layer was separated and washed with saturated $NaHCO_3$ and H_2O, dried over anhydrous Na_2SO_4, and concentrated to dryness.The oil obtained was purified by FC, using 1:1 hexane/ethyl acetate as eluent. Compound **9** (0.15 g, 60%) was isolated as a colourless oil. IR (ν): 3299, 2953, 1739, 1654, 1543, 1385, 1247, 1037. ^{1}H NMR ($CDCl_3$), δ: 1.11 (1H, dt, J_d = 13.41, J_t = 6.76, 5-HH), 1.97 (3H, s, CH_3CON), 2.05 (3H, s, CH_3COO), 2.21 (1H, dt, J_d = 13.41, J_t = 8.67, 5-HH), 2.90-3.03 (2H, m, 4-H + 1-H), 3.19 (1H, dt, J_d = 13.34, J_t = 5.94, 4-CHH), 3.96 (1H, dt, J_d = 13.34, J_t = 6.22, 4-CHH), 3.96 (1H, part A of a ABM system, J_{AB} =10.73, J_{AM} = 6.40, 1-CHH), 4.01 (1H, part B of a ABM system ABM, J_{BA} = 10.73, J_{BM} = 6.40, 1-CHH), 5.67-5.74 (2H, m, 3-H + 2-H). ^{13}C NMR ($CDCl_3$), δ: 171.57, 161.80, 134.29, 133.58, 68.20, 68.11, 46.05, 45.49, 31.02, 23.69, 21.35. HRMS *m/z*: Calcd for $C_{11}H_{17}NO_3$: 211.1209. Found: 211.1201.

***cis*-4-[(2-Amino-6-chloropyrimidin-4-yl)aminomethyl]-2-cyclopentenylmethanol (10).** A solution of **6** (0.67 g, 5.27 mmol), 2-amino-4,6-dichoropyrimidine (1.29 g, 7.78 mmol) and dry triethylamine (3.5 mL) in dry 1-butanol (21 mL) was refluxed under a dry atmosphere for 48 h. The reaction mixture was cooled, the solvent was remove *in vacuo* and the residue remaining was column chromatographed (eluant 30:1 chloroform/methanol). The crude residue recovered from the eluate was redissolved in dry acetone, and the mixture was filtered and the solvent was removed *in vacuo*, affording compound **10** (0.9 g, 68%) as an oil. ^{1}H NMR ($CDCl_3$), δ: 1.43 (1H, dt, J_d = 13.64, J_t = 5.40, 5-HH), 2.26 (1H, dt, J_d = 13.64, J_t = 9.43, 5-HH), 2.93-3.07 (2H, m, 4-H + 1-H), 3.25-3.30 (3H, m, partial D_2O exch., 4-CH_2 + OH), 3.64 (1H, part A of a ABM system, J_{AB} = 10.60, J_{AM} = 4.32, 1-CHH), 3.71 (part B of a AMB system J_{BA} = 10.60, J_{BM} = 4.42, 1-CHH), 4.90 (3H, bs, D_2O exch., NH + NH_2), 5.70-5.78 (2H, m, 2-H + 3-H), 5.77 (1H, s, arom). ^{13}C NMR ($CDCl_3$), δ: 164.58, 164.53, 162.27, 135.11, 133.95, 93.12, 67.31, 48.17, 46.74, 45.35, 30.26. HRMS *m/z*: Calcd for $C_{11}H_{15}ClN_4O$: 254.0935. Found: 254.0927.

***cis*-4-{[2-Amino-6-chloro-5-(4-chlorophenylazo)pyrimidin-4-yl]aminomethyl}-2-cyclopentenyl methanol (11).** 4-Chloroaniline (0.48 g, 4.06 mmol) in 3N HCl (8 mL) was treated at 0°C with sodium nitrite (0.28 g, 4.06 mmol) in water (3.5 mL). The diazonium salt obtained was added to a mixture of **10** (0.85 g, 3.33 mmol), acetic acid (16 mL), water (16 mL) and sodium acetate trihydrate (6.5 g) and stirred overnight at room temperature .The precipitate formed was filtered out, washed with water until the washings were neutral, and dried to afford **11** (1.00 g, 76%) as a yellow solid. An analytical sample was obtained by recrystallization from acetone/water. M.p. 213-215°C. ^{1}H NMR ($CDCl_3$), δ: 1.39 (1H, dt, J_d = 13.38, J_t = 5.82, 5-HH), 2.01-2.17 (1H, m, D_2O exch., OH), 2.25 (1H, dt, J_d = 13.38, Jt = 8.93, 5-HH), 2.96-3.12 (1H, m, 4-H), 3.09-3.22 (1H, m, 1-H), 3.57-3.67 (4H, m, 1-CH_2 + 4-CH_2), 5.20-5.31 (2H, m, partial D_2O exch., 3-H + NH), 5.75-5.84 (3H, m, partial D_2O exch., 2-H + NH_2), 7.43 (2H, d, J = 8.71, 3'-H + 5'-H), 7.72 (2H, d, J = 8.71, 2'-H + 6'-H). ^{13}C NMR ($CDCl_3$), δ: 166.27, 161.15, 155.51, 151.40, 135.59, 135.13, 133.94, 129.79, 123.40, 120.45, 67.54, 48.33, 45.57, 45.43, 30.35. Anal. Calcd. for $C_{17}H_{18}Cl_2N_6O$: C, 51.92; H, 4.61; N, 21.37. Found: C, 52.14, H, 4.73; N, 21.17.

***cis*-4-[(2,5-Diamino-6-chloropyrimidin-4-yl)aminomethyl]-2-cyclopentenylmethanol (12).** A mixture of **11** (1.0 g, 2.54 mmol), zinc powder (1.66 g, 25.4 mmol), acetic acid (0.8 mL), water (37 mL) and ethanol (37 mL) was refluxed under argon for 3 h. Then, the reaction mixture was filtered, the solvent was removed *in vacuo* and the residue was purified by FC using 15:1 chloroform/methanol as eluant. Compound **12** (0.56 g, 82 %) was isolated as a reddish oil. ^{1}H NMR (DMSO), δ: 1.48 (1H, dt, J_d = 13.80, J_t = 4.94, 5-HH), 2.22 (1H, dt, J_d = 13.80, J_t = 9.56, 5-HH), 2.79 (1H, m, D_2O exch., OH), 2.92-2,98 (1H, m, 4-H), 3.01-3.14 (1H, m, 1-H), 3.35-3.43 (1H, m, 4-CHH), 3.49-3.60 (1H, m, 4-CHH), 3.64 (1H, part A of a ABM system, J_{AB} = 10.90, J_{AM} = 3.95, 1-CHH), 3.68 (1H, part B of a ABM system, J_{BA} = 10.90, J_{BM} = 4.16, 1-CHH), 4.83 (2H, bs, D_2O exch., NH_2), 5.71-5.84 (3H, m, partial D_2O exch., 3-H + 2-H + NH). ^{13}C NMR ($CDCl_3$), δ: 159.63, 158.27, 148.63,

135.07, 133.93, 111.60, 67.53, 49.07, 45.76, 45.44, 30.40. HRMS *m/z*: Calcd for $C_{11}H_{16}ClN_5O$: 269.1044. Found: 269.1048.

***cis*-4-(2-Amino-6-chloro-9*H*-purin-9-ylmethyl)-2-cyclopentenylmethanol (13).** A mixture of **12** (0.56 g, 2.08 mmol), triethyl orthoformate (12 mL) and 12N HCl (0.50 mL) under argon was stirred overnight at room temperature. The mixture was concentrated to dryness *in vacuo*, and 0.5N HCl (15 mL) was added to the residue and stirred for 1h. The mixture was adjusted to pH 8 with 1N NaOH, and the solvent was evaporated *in vacuo*. The crude product (1.57 g) was purified by FC, using 20:1 chloroform/methanol as eluant. Compound **13** (0.32 g, 55 %) was isolated as a white foam. ^{1}H NMR (DMSO-d_6), δ: 1.16 (1H, dt, J_d = 13.19, J_t = 6.63, 5-H<u>H</u>), 2.00 (1H, dt, J_d = 13.19, J_t = 8.56, 5-H<u>H</u>), 2.63-2.80 (1H, m, 1-H), 3.15-3.22 (3H, m, 1-CH_2 + 4-H), 3.99 (1H, part A of a ABM system, J_{AB} = 13.28, J_{AM} = 7.19, 4-C<u>H</u>H), 4.05 (1H, part B of a ABM system, J_{BA} = 13.28, J_{BM} = 7.27, 4-CH<u>H</u>), 4.55 (1H, t, J = 10.52, D_2O exch., OH), 5.67 (1H, dt, J_d = 5.67, J_t = 2.08, 3-H), 5.77 (1H, dt, J_d = 5.67, J_t = 2.15, 2-H), 6.88 (2H, bs, D_2O exch., NH_2), 8.10 (1H, s, arom.). ^{13}C NMR (DMSO-d_6), δ: 160.15, 154.64, 149.70, 143.74, 135.39, 132.16, 123.62, 65.54, 48.90, 45.76, 41.86, 30.60. HRMS *m/z*: Calcd for $C_{12}H_{14}ClN_5O$: 279.0887. Found: 279.0882.

***cis*-2-Amino-6,9-dihydro-9-[3-(hydroxymethyl)-2-cyclopentenylmethyl]-1*H*-purin-6-one (14).** A mixture of **13** (0.32 g, 1.14 mmol) and 0.33N NaOH (25 mL) was refluxed for 5 h. The solvent was removed *in vacuo* and the residue was purified by FC, using 10:1 chloroform/methanol as eluant. Compound **14** (0.24 g, 80 %) was isolated as a white solid. An analytical sample was obtained by recrystallization from 2:1 methanol/water, m.p. 263-265°C. ^{1}H NMR (DMSO-d_6), δ: 1.16 (1H, dt, J_d = 13.27, J_t = 6.62, 5-H<u>H</u>), 2.00 (1H, dt, J_d = 13.27, J_t = 8.65, 5-H<u>H</u>), 2.69-2.74 (1H, m, 4-H), 3.15-3.28 (3H, m, 4-CH_2 + 1-H), 4.08 (1H, part A of a ABM system, J_{AB} = 13.56, J_{BM} = 7.17, 1-C<u>H</u>H), 4.15 (1H, part B of a ABM system, J_{BA} = 13.56, J_{BM} = 6.41, 1-CH<u>H</u>), 4.53 (1H, t, J = 5.28, D_2O exch., OH), 5.60 (1H, dt, J_d = 5.67, J_t = 2.09, 3-H), 5.76 (1H, dt, J_d = 5.67, J_t = 2.06, 2-H), 7.65 (1H, s, arom.), 10.51 (1H, bs, D_2O exch., NH). ^{13}C NMR (DMSO-d_6), δ: 157.17, 153.86, 151.63, 137.99, 135.20, 132.32, 116.70, 65.59, 48.90, 47.84, 46.04, 30.60. Anal. Calcd. for $C_{12}H_{15}N_5O_2$: C, 55.16; H, 5.79; N, 26.80. Found: C, 55.34, H, 5.89; N, 20.77.

***cis*-4-(6-Chloro-9-*H*-purin-9-ylmethyl)-2-cyclopentenylmethyl acetate (15)** Diethyl azodicarboxylate (0.82 mL, 5.21 mmol) was added to a suspension of triphenylphosphine (1.29 g, 4.92 mmol) and 6-chloropurine (0.78 g, 5.05 mmol) in tetrahydrofuran (33 mL). The mixture was stirred at room temperature for 1 h, after which a solution of **3** (0.70 g, 4.14 mmol) in tetrahydrofuran (11 mL) was added and stirring was continued at 40°C. Tlc monitoring indicated the reaction to be complete after 24 h, whereupon he solvent was evaporated *in vacuo* and the solid residue (3.92 g) was flash-chromatographed, using 3:2 ethyl acetate/hexane as eluant. Evaporation of the eluates afforded (in order of elution) diethyl hydrazodicarboxylate, compound **15** (0.30 g), and a solid (1.20 g) indicated by ^{1}H NMR to be a 7:1 (molar ratio) mixture of triphenylphosphine oxide and **15** (estimated total yield, 36%). ^{1}H NMR (DMSO-d_6), δ: 1.32 (1H, dt, J_d = 13.32, J_t = 6.99, 5-H<u>H</u>), 2.04 (3H, s,

CH_3), 2.24 (1H, dt, J_d =13.32, J_t = 8.61, 5-HH), 3.00-3.06 (1H, m, 1-H), 3.34-3.40 (1H, m, 4-H), 3.94 (1H, part A of a ABM system, J_{AB} = 10.88, J_{BM} = 5.94, 1-CHH), 4.01 (1H, part B of a ABM system J_{BA} = 10.88, J_{BM} = 6.53, 1-CHH), 4.46 (1H, part A of a ABM system J_{AB} = 14.13, J_{AM} = 7.21, 4-CHH), 4.48 (1H, part B of a ABM system J_{BA} = 14.13, J_{BM} = 7.36, 4-CHH), 5.73 (1H, dt, J_d = 5.73, J_t = 2.02, 2-H), 5.84 (1H, dt, J_d = 5.73, J_t = 2.16, 3-H), 8.14 and 8.74 (2H, 2s, arom). ^{13}C NMR (DMSO-d_6), δ: 171.65, 152.89, 151.80, 149.32, 147.74, 135.02, 131.37, 130.86, 66.62, 48.91, 48.01, 45.99, 31.55, 21.37. HRMS *m/z*: Calcd for $C_{14}H_{15}ClN_4O_2$: 306.0884. Found: 306.0890.

***cis*-4-(6-Amino-9*H*-purin-9-ylmethyl)-2-cyclopentenylmethanol (16)** A suspension of **15** (0.30 g, 0.98 mmol) in methanol (3 mL) a pressurized reactor was cooled in an acetone/CO_2 bath and treated with liquid ammonia (3 mL). The reactor was sealed and the mixture was heated at 75°C for 48 h. The solvent was evaporated and the white solid obtained was recrystallized from methanol, affording **16** (0.22g, 92%). M.p. 179-181°C. ^{1}H NMR (DMSO-d_6), δ: 1.18 (1H, dt, J_d = 13.22, J_t = 6.63, 5-HH), 1.98 (1H, dt, J_d = 13.22, J_t = 8.60, 5-HH), 2.68-2.73 (1H, m, 1-H), 3.15-3.25 (3H, m, 1-CH_2 + 4-H), 4.07 (1H, part A of a ABM system, J_{AB} = 13.60, J_{AM} = 7.23, 4-CHH), 4.14 (1H, part B of a ABM system, J_{BA} = 13.60, J_{BM} = 6.38, 4-CHH), 4.57 (1H, t, J = 5.30, D_2O exch., OH), 5.63 (1H, dt, J_d = 5.67, J_t = 2.03, 2-H), 5.75 (1H, dt, J_d = 5.67, J_t = 2.03, 3-H), 7.18 (2H, s, D_2O exch., NH_2), 8.11 and 8.12 (2H, 2s, arom.). ^{13}C NMR (DMSO-d_6), δ: 156,30, 152.72, 150.06, 141.30, 135.17, 132.36, 118.99, 65.63, 48.89, 47.97, 46,21, 30.59. Anal. Calcd. for $C_{12}H_{15}N_5O$: C, 58.76; H, 6.16; N, 28.55. Found: C, 58.64, H, 6.19; N, 28.43.

***cis*-6,9-Dihydro-9-[4-(hydroxymethyl)-2-cyclopentenylmethyl]-1*H*-purin-6-one (17)** The mixture of triphenylphosphine oxide/compound **15** isolated above (0.91 g, equivalent to 0.12 g of **15**, 0.40 mmol) was refluxed in 0.33N NaOH (14 mL) for 5 h. The solvent was evaporated *in vacuo* gave a residue (1.09 g), which was flash-chromatographed using 5:1 chloroform/methanol as eluant. Compound **17** (85 mg, 80%) was isolated as a white solid, which was recrystallized from a methanol/water solvent pair, m.p. 251-253°C. ^{1}H NMR (DMSO-d_6), δ: 1.16 (1H, dt, J_d = 13.27, J_t = 6.62, 5-HH), 2.00 (1H, dt, J_d = 13.27, J_t = 8.65, 5-HH), 2.68-2.74 (1H, m, 4-H), 3.15-3.28 (3H, m; CH_2OH + 1-H), 4.08 (1H, part A of a ABM system, J_{AB} = 13.56, J_{AM} = 7.17, 1-CHH), 4.15 (1H, part B of a ABM system, J_{BA} = 13.56, J_{BM} = 6.48, 1-CHH), 4.53 (1H, t; J = 5.28, D_2O exch., OH), 5.62 (1H, dt, J_d = 5.68, J_t = 2.06, 3-H), 5.76 (1H, dt, J_d = 5.68, J_t = 2.09, 2-H), 8.03 (1H, d, J = 13.08, 2-H, arom), 8.28 (1H, s, 8-H, arom), 12.23 (1H, s, D_2O exch., NH). ^{13}C NMR (DMSO-d_6), δ: 157.03, 148.85, 145.71, 140.78, 135.31, 132.15, 124.17, 65.58, 48.87, 48.26, 46.32, 31.45. Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.60, H, 5.91; N, 22.53.

Acknowledgements

The authors thank the Spanish Ministry of Education and Science (MEC-DGICYT, PB94-0617) and the Xunta de Galicia (XUGA 20307B94) for financially supporting this work.

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