Carbocyclic Analogues of Nucleosides from bis-(Hydroxymethyl)-cyclopentane: Synthesis, Antiviral and Cytostatic Activities of Adenosine, Inosine and Uridine Analogues

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Six new carbocyclic nucleosides were prepared by constructing a purine base (in compounds 9—11) or pyrimidine base (in 6—8) on the amino groups of (±)-(1β,2α,4β)-4-amino-1,2-cyclopentanedimethanol (4) and (±)-(1β,3α,4β)-4-amino-1,3-cyclopentanedimethanol (5), and their activities against a variety of viruses and tumour cell lines were determined.

Key words carbocyclic nucleoside; adenosine analogue; uridine analogue; antiviral activity; cytostatic activity

Nucleoside analogues that inhibit the reverse transcriptase of human immunodeficiency virus (HIV) continue to be the cornerstone of AIDS therapy.[1)] Furthermore, although side effects limit the use of 3′-azido-3′-deoxythymidine (AZT), 2′,3′-dideoxyinosine (ddI) and 2′,3′-dideoxycytidine (ddC),[2—4)] and resistance to single agents has emerged,[5,6)] nucleoside analogues are still the compounds attracting most attention in the search for nontoxic agents capable of selectively inhibiting the replication of HIV and other viruses. In particular, carbocyclic analogues of nucleosides (CANs), which have no labile glycoside link between the base and the carbocycle replacing the sugar of true nucleosides, could offer an attractive *in vivo* stability advantage over the 2′,3′-dideoxynucleosides, as well as being more lipophilic (and hence potentially more readily absorbed) because of the replacement of the endocyclic oxygen by a methylene group.

Among CANs with anti-HIV activity are the 2′,3′-unsaturated compounds 2′,3′-didehydro-ddA,[7)] 2′,3′-didehydro-2′,3′-dideoxyguanosine (carbovir)[8)] (**1**) and abacavir (Ziagen®) (**2**), which has better oral bioavailability and better penetration into the central nervous system than the other two and is currently being used in combination with other antiretroviral drugs to treat HIV infection in adults.[7,9—11)]

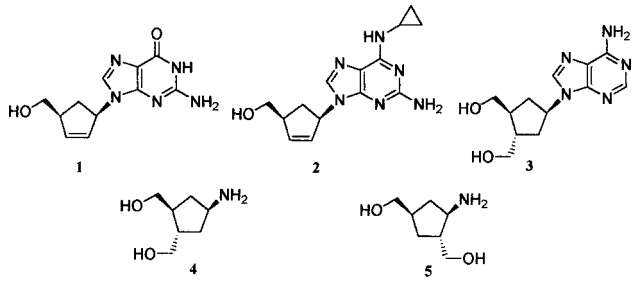
However, reports of significant antiviral activity by nucleoside analogues with more than one hydroxymethyl group on the "sugar" ring (whether furan[12,13)] or cyclobutane[14,15)]) soon led to investigation of a number of bis(hydroxymethyl)cyclopentane derivatives.[16—18)] It was found that although (3*S*,4*S*)- and *rac*-bis(hydroxymethyl)cyclopentyl adenine **3** are inactive against HIV-1,[16,17)] (3*S*,4*S*)-**3** is active against type 1 herpes simplex virus (HSV-1), with an IC_{50} of less than 0.0001 μg/ml.[19)]

In this work we extended the search for bis(hydroxymethyl)cyclopentanes with antiviral and antitumour activities by preparing and screening seven that were chosen with a view to analysing the influence of various structural parameters on their biological activity. All these compounds were prepared by construction of the heterocyclic base on the amino group of either (±)-(1β,2α,4β)-4-amino-1,2-cyclopentanedimethanol (**4**) or (±)-(1β,3α,4β)-4-amino-1,3-cyclopentanedimethanol (**5**). Six—the uridine analogues **6**—**8**, the inosine analogue **9**, and the adenosine analogues **10** and **11** (see Charts 1, 2)—have not been reported previously.

Preparation of the uridine analogues was based on the propenoylurea variant of Shaw's synthesis of pyrimidine-2,4-(1*H*,3*H*)-diones,[20)] to which end 3-ethoxypropenoyl isocyanate was prepared by means of a two-step procedure that for this kind of analogues has performed better[21)] than alternative methods.[22)] Since the isocyanate is unstable, the resulting reaction solution was added, without prior isolation of the isocyanate, to the amino alcohols **4** and **5**. The resulting propenoylureas, **12** and **13**, respectively, were then cyclized under conventional acidic conditions,[22)] affording compounds **14** and **7** in practically quantitative yield. These compounds were finally converted into their 5-iodo derivatives **6** and **8** by treatment with iodine in a mixture of dioxane and nitric acid.[23)]

Compounds **9**—**11** were prepared using standard chemistry for purine CANs[24)] (Chart 1): amino alcohol **4** was condensed with 5-amino-4,6-dichloropyrimidine, the resulting diamine **15** was cyclized with ethyl orthoformate to obtain the key intermediate **16** (in 84% yield from **4**), and this 9-substituted 6-chloropurine was further transformed into the final products in yields of 86—98%. Hydrolysis with 1 N HCl gave the inosine analogue **9**; nucleophilic substitution by ammonia gave the adenosine analogue **3**; and treatment with cyclopropylamine or isopropylamine in refluxing ethanol gave the *N*-alkyladenosine analogues **10** and **11**, respectively.

Using previously established procedures,[25,26)] the *in vitro* antiviral activities of compounds **6**—**11** were determined against a variety of DNA and RNA viruses, and their cytotoxicities for the host cell lines, were assayed in parallel with



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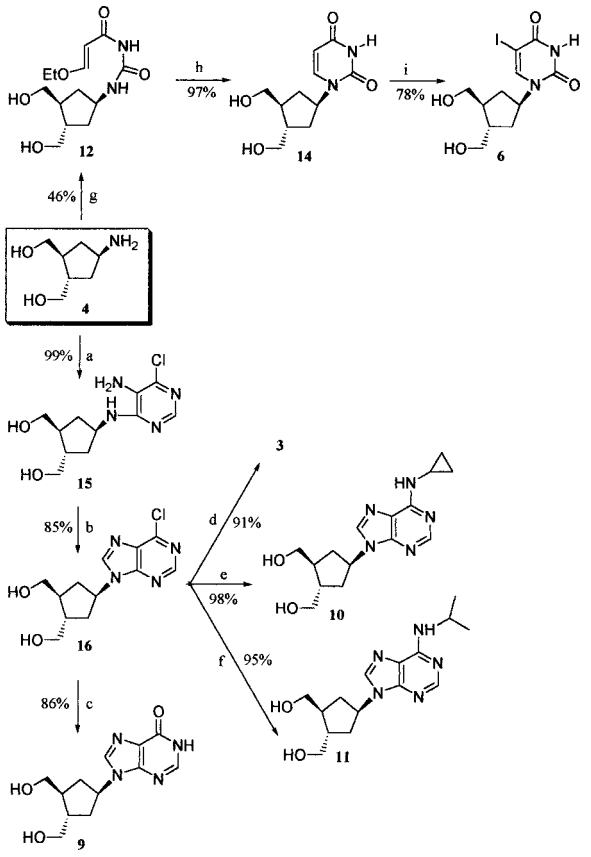
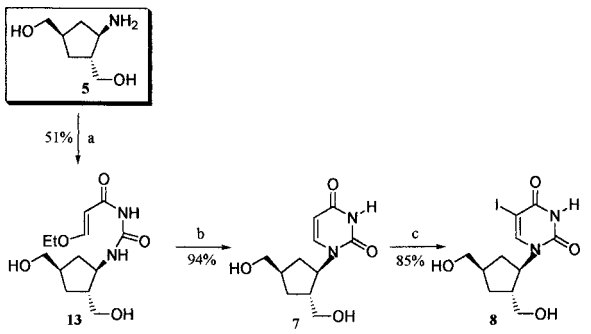


(a) 5-Amino-4,6-dichloropyrimidine, *n*-BuOH, Et_3N; (b) $HC(OEt)_3$, 12 N HCl; (c) 1 N HCl, reflux; (d) 14 N NH_4OH, reflux; (f) $^iPrNH_2$, EtOH reflux; (g) ethoxypropenoyl isocyanate, DMF, −15 °C; (h) 2 N H_2SO_4; (i) I_2/HNO_3.

Chart 1



(a) Ethoxypropenoyl isocyanate, DMF, −15 °C; (b) 2 N H_2SO_4; (c) I_2/HNO_3.

Chart 2

those of standard drugs with known antiviral activities. The viruses and cells used were type 1 herpes simplex virus (strain KOS), type 2 herpes simplex virus (strain G), vaccinia virus, vesicular stomatitis virus and thymidine-kinase-deficient (TK^-) KOS in E_6SM cells; type 3 parainfluenza virus, type 1 reovirus, Sindbis virus, Coxsackie B4 virus and Punta Toro virus in Vero cells; respiratory syncytial virus in HeLa cells; cytomegalovirus (strains AD-169 and DAVIS), varicella zoster virus (strains OKA and YS) and thymidine-kinase-deficient (TK^-) varicella zoster virus (strains 07/1 and YS/R) in human embryonic lung (HEL) cells; and HIV-1 and HIV-2 in human T-lymphocyte (CEM) cells (at compound concentrations up to 100 μg/ml). At subtoxic concentrations the new compounds generally showed no activity against any of these viruses. The antitumoral activities of compounds **6**—**11** were assayed against murine leukaemia cells (L1210/0) and human T-lymphocytes (Molt4/C8 and CEM/0) using procedures described elsewhere.[26] The concentrations required to reduce cell growth by 50% (IC_{50}) were >200 μg/ml in all cases.

Experimental

Melting points are uncorrected and were determined in a Reichert Kofler Thermopan or in capillary tubes in a Büchi 510 apparatus. Infrared spectra of samples in KBr discs (solids) or of films between NaCl plates (oils) were recorded in a Perkin-Elmer 1640 FTIR spectrophotometer. ^{1}H-NMR spectra (300 MHz) and ^{13}C-NMR spectra (75 MHz) were recorded in a Bruker AMX 300 spectrometer using tetramethylsilane (TMS) as internal reference (chemical shifts in δ values, J in Hz). Mass spectra were recorded on a Kratos MS-59 spectrometer. Microanalyses were performed in a Perkin-Elmer 240B element analyser by the Microanalysis Service of the University of Santiago. Flash chromatography was performed on silica gel (Merck 60, 230—240 mesh) and analytical TLC on pre-coated silica gel plates (Merck 60 F254, 0.25 mm). Reagents and solvents were supplied by Aldrich Chemical Co. Starting materials **4** and **5** were prepared as previously described.[27]

(±)-(1β,2α,4β)-4-[(5-Amino-6-chloropyrimidin-4-yl)amino]-1,2-cyclopentanedimethanol (15) A solution of (±)-**4** (0.1 g, 0.69 mmol), 5-amino-4,6-dichloropyrimidine (0.17 g, 1.04 mmol) and triethylamine (0.9 ml) in dry *n*-butanol (8 ml) was refluxed under argon for 48 h. After cooling, the solvents were removed under reduced pressure and purification of the residue by column chromatography with 10 : 1 CH_2Cl_2/MeOH as eluent afforded (±)-**15** as a viscous paste (0.19 g, 99%). IR (film) γ_{max}: 3359, 3300, 2937, 1704, 1651, 1583, 1505, 1470, 1422, 1231 cm^{-1}. ^{1}H-NMR (DMSO-d_6), as previously reported.[16] ^{13}C-NMR (DMSO-d_6) δ: 30.61 and 36.65 (C3+C5), 38.69 and 47.05 (C1+C2), 54.13 (C4), 63.04 (CH_2O), 65.63 (CH_2O), 123.71 ($C5_{arom}$), 137.42 ($C4_{arom}$), 145.82 ($C2_{arom}$), 152.98 ($C6_{arom}$). Electron impact (EI)-MS *m/z* (%): 273 (12, $(M+1)^+$), 272 (30, M^+), 256 (20), 241 (33), 144 (100), 127 (6). *Anal.* Calcd for $C_{11}H_{17}ClN_4O_2$: C, 48.44; H, 6.28; Cl, 13; N, 20.54. Found: C, 48.55; H, 6.33; Cl, 12.88; N, 20.48.

(±)-(1β,2α,4β)-4-(6-Chloro-9*H*-purin-9-yl)-1,2-cyclopentanedimethanol (16) A mixture of (±)-**15** (0.76 g, 2.79 mmol), triethyl orthoformate (16.2 ml, 144.3 mmol) and 12 N HCl (0.84 ml) was stirred at room temperature for 18 h and then condensed to dryness under reduced pressure. The residue was treated for 2 h with 0.5 N HCl (25 ml), this mixture was brought to pH 7 with 1 N NaOH, the solvent was evaporated, and the semisolid residue was chromatographed on silica gel with 10 : 1 $CHCl_3$/MeOH as eluent, affording (±)-**16** as a viscous paste (0.67 g, 85%). IR (film) γ_{max}: 3379, 2937, 1592, 1557, 1494, 1394, 1336, 1200 cm^{-1}. ^{1}H-NMR (DMSO-d_6), as previously reported.[16] ^{13}C-NMR (DMSO-d_6) δ: 29.99 and 36.08 (C3+C5), 38.74 and 45.33 (C1+C2), 58.90 (C4), 62.70 (CH_2O), 65.28 (CH_2O), 131.62 ($C5_{arom}$), 147.10 ($C8_{arom}$), 149.31 ($C6_{arom}$), 151.49 ($C2_{arom}$), 152.23 ($C4_{arom}$). EI-MS *m/z* (%): 283 (1, $(M+1)^+$), 282 (7, M^+), 251 (16), 222 (2), 181 (18), 155 (100), 119 (13). *Anal.* Calcd for $C_{12}H_{15}ClN_4O_2$: C, 50.98; H, 5.35; Cl, 12.54; N, 19.82. Found: C, 50.89; H, 5.39; Cl, 12.67; N, 19.68.

(±)-6,9-Dihydro-9[(1β,3α,4β)-3,4-bis(hydroxymethyl)cyclopentyl]-1*H*-purin-6-one (9) (±)-**16** (0.15 g, 0.53 mmol) was refluxed for 4 h in 1 N HCl (15 ml). After cooling, the solvent was removed under reduced pressure, the solid residue (0.28 g) was suspended in water (10 ml), and this suspension was brought to pH 7 with 1 N NaOH. The solvents were then evaporated, and the semisolid residue was chromatographed on silica gel with 10 : 3 CH_2Cl_2/MeOH as eluent, which afforded (±)-**9** as a white solid (0.12 g, 86%). An analytic sample was obtained by recrystallization from ethanol. mp 208—210 °C. IR (KBr) γ_{max}: 3384, 2868, 1694, 1591, 1546, 1415, 1340, 1217 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.73—1.76 (2H, m), 1.80—1.92 (1H, m), 2.20—2.29 (2H, m), 2.56—2.63 (1H, m), 3.34—3.49 (4H, m, 2×CH_2O), 4.37—4.58 (3H, m, 1-H+2×OH (D_2O exchang.)), 8.07 and 8.22 (2H, 2s, $(2\text{-H}+8\text{-H})_{arom}$), 12.30 (1H, br s, D_2O exchang., 1-H_{arom}). ^{13}C-NMR (DMSO-d_6) δ: 35.46 and 41.85 (C2+C5), 44.03 and 51.07 (C3+C4), 63.04 (C1), 67.65 (CH_2O), 70.61 (CH_2O), 129.96 ($C5_{arom}$), 144.87 ($C8_{arom}$), 150.69 ($C4_{arom}$), 153.96 ($C2_{arom}$), 162.31 ($C6_{arom}$). EI-MS *m/z* (%): 265 (5, $(M+1)^+$), 264 (33, M^+), 247 (3), 233 (21), 194 (18), 163 (26), 137 (100), 109 (25). *Anal.* Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 21.20. Found: C, 54.41; H, 5.99; N, 21.24.

(±)-(1β,2α,4β)-4-(6-Amino-9*H*-purin-9-yl)-1,2-cyclopentanedimethanol

(3) (±)-**16** (0.24 g, 0.85 mmol) was refluxed for 15 min in concentrated NH_4OH (29 ml). After cooling, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel with 4 : 1 EtOAc/MeOH as eluent, which afforded (±)-**3** as a white solid (0.2 g, 91%). An analytic sample was obtained by recrystallization from ethanol. mp 182—184 °C (lit.[16] mp 182—183 °C). IR (KBr) γ_{max}: 3370, 3254, 2933, 1684, 1614, 1570, 1477, 1308, 1217 cm^{-1}. ^{1}H-NMR (DMSO-d_6), as previously reported.[16] ^{13}C-NMR (DMSO-d_6) δ: 30.29 and 36.10 (C3+C5), 38.77 and 45.54 (C1+C2), 57.54 (C4), 62.42 (CH_2O), 65.45 (CH_2O), 119.23 ($C5_{arom}$), 140.33 ($C8_{arom}$), 149.20 ($C4_{arom}$), 152.42 ($C2_{arom}$), 156.32 ($C6_{arom}$). EI-MS *m*/*z* (%): 264 (7, $(M+1)^+$), 263 (44, M^+), 246 (38), 232 (52), 162 (61), 136 (100), 108 (46). *Anal.* Calcd for $C_{12}H_{17}N_5O_2$: C, 54.74; H, 6.51; N, 26.60. Found: C, 54.81; H, 6.65; N, 26.48.

(±)-(1β,2α,4β)-4-(6-Cyclopropylamino-9*H*-purin-9-yl)-1,2-cyclopentanedimethanol (10) A mixture of (±)-**16** (0.19 g, 0.67 mmol) and cyclopropylamine (0.49 ml, 7.08 mmol) in dry ethanol (15 ml) was refluxed under argon for 5 h and then condensed to dryness. The resulting residue was chromatographed on silica gel with 4 : 1 EtOAc/MeOH as eluent, which afforded (±)-**10** as a white solid (0.2 g, 98%). An analytic sample was obtained by recrystallization from 3 : 1 EtOAc/ether. mp 78—80 °C. IR (KBr) γ_{max}: 3258, 3105, 2930, 2344, 1618, 1527, 1440, 1381, 1236, 1130 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.56—0.65 (2H, m, cyclopropyl CH_2), 0.67—0.73 (2H, m, cyclopropyl CH_2), 1.64—1.75 (2H, m), 1.89—1.93 (1H, m), 2.11—2.21 (2H, m), 2.59—2.61 (1H, m), 2.95—3.11 (1H, m), 3.27—3.33 (2H, m, CH_2O), 3.39—3.41 (2H, m, CH_2O), 4.54—4.63 (3H, m, 4-H+2×OH (D_2O exchang.)), 7.80—7.81 (1H, m, NH), 8.19 and 8.21 (2H, 2s, (2-H+8-H)$_{arom}$). ^{13}C-NMR (DMSO-d_6) δ: 7.81 (CH_2–CH_2), 23.94 (CHNH), 30.29 and 36.10 (C3+C5), 38.77 and 45.55 (C1+C2), 57.56 (C4), 62.45 (CH_2O), 65.47 (CH_2O), 120.01 ($C5_{arom}$), 140.13 ($C8_{arom}$), 149.11 ($C6_{arom}$), 152.33 ($C2_{arom}$), 155.92 ($C4_{arom}$). EI-MS *m*/*z* (%): 304 (13, $(M+1)^+$), 303 (70, M^+), 288 (100), 174 (47), 160 (77). *Anal.* Calcd for $C_{15}H_{21}N_5O_2$: C, 59.39; H, 6.98; N, 23.09. Found: C, 59.45; H, 6.87; N, 23.18.

(±)-(1β,2α,4β)-4-(6-*N*-Isopropylamino-9*H*-purin-9-yl)-1,2-cyclopentanedimethanol (11) A mixture of (±)-**16** (0.19 g, 0.67 mmol) and isopropylamine (0.5 ml, 7.63 mmol) in dry ethanol (15 ml) was refluxed under argon for 8 h and then condensed to dryness under reduced pressure. The resulting residue was chromatographed on silica gel with 20 : 3 EtOAc/MeOH as eluent, which afforded (±)-**11** as a white solid (0.19 g, 95%). An analytic sample was obtained by precipitation with ether. mp 135—136 °C. IR (KBr) γ_{max}: 3348, 3258, 2967, 2867, 1614, 1574, 1471, 1404, 1365, 1297, 1164 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (6H, d, *J*=6.49 Hz, 2×CH_3), 1.58—1.79 (2H, m), 1.84—1.95 (1H, m), 2.08—2.21 (2H, m), 2.57—2.65 (1H, m), 3.25—3.27 (2H, m, CH_2O), 3.35—3.37 (2H, m, CH_2O), 4.19—4.34 (1H, m, C<u>H</u>(CH_3)$_2$), 4.53—4.69 (3H, m, 4-H+2×OH (D_2O exchang.)), 7.37 (1H, d, *J*=8.12 Hz, NH), 8.07 and 8.11 (2H, 2s, (2-H+8-H)$_{arom}$). ^{13}C-NMR (DMSO-d_6) δ: 23.51 (2×CH_3), 30.29 and 36.12 (C3+C5), 38.73 and 45.55 (C1+C2), 42.23 (<u>C</u>H(CH_3)$_2$), 57.53 (C4), 62.46 (CH_2O), 65.46 (CH_2O), 120.02 ($C5_{arom}$), 139.88 ($C8_{arom}$), 149.13 ($C6_{arom}$), 152.52 ($C2_{arom}$), 154.32 ($C4_{arom}$). EI-MS *m*/*z* (%): 306 (6, $(M+1)^+$), 305 (30, M^+), 288 (32), 274 (33), 177 (50), 162 (100), 135 (55). *Anal.* Calcd for $C_{15}H_{23}N_5O_2$: C, 59.00; H, 7.59; N, 22.93. Found: C, 58.88; H, 7.46; N, 22.79.

(±)-*N*-[(1β,3α,4β)-3,4-bis(Hydroxymethyl)cyclopentyl]-*N*′-(3-ethoxypropenoyl)urea (12) Dry benzene (321 ml) was added in the dark, under argon, to silver cyanate (48 g) that had previously been dried *in vacuo* over P_2O_5 at 100 °C. The resulting suspension was refluxed with vigorous stirring for 30 min, after which a solution of 3-ethoxypropenoyl chloride (19.28 g, 160 mmol) in dry benzene (60 ml) was added dropwise. The resulting mixture was refluxed with vigorous stirring for a further 30 min, vigorously stirred at room temperature for 3 h, and then left to settle. A sample of the supernatant (16 ml, theoretically containing 6.62 mmol of 3-ethoxypropenoyl isocyanate) was transferred to a dropping funnel and added dropwise under argon to a solution of (±)-**4** (0.64 g, 4.41 mmol) in dry DMF (21 ml) at −15 °C. The resulting mixture was left for 1 h to reach room temperature and was then stirred overnight and concentrated under reduced pressure (oil pump) at a temperature below 40 °C. Removal of the solvents by repeated co-evaporation with ethanol left a solid that when chromatographed on silica gel with 30 : 1 EtOAc/MeOH as eluent afforded compound (±)-**12** (0.58 g, 46%) as a white solid. An analytic sample was obtained by recrystallization from 4 : 1 cyclohexane/EtOAc. mp 92—95 °C. IR (KBr) γ_{max}: 3252, 3100, 2936, 1681, 1610, 1557, 1499, 1396, 1346, 1253, 1169, 1133 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.97—1.06 (1H, m), 1.10 (3H, t, *J*=7.01 Hz, CH_3), 1.31—1.42 (2H, m), 1.62—1.75 (1H, m), 1.83—2.05 (2H, m), 3.11—3.28 (4H, m, 2×CH_2O), 3.52—3.68 (1H, m, 1-H), 3.79 (2H, c, *J*=7.04 Hz, C<u>H</u>$_2$CH$_3$), 4.35 (2H, br s, D_2O exchang., 2×OH), 5.63 (1H, d, *J*=12.34 Hz, C<u>H</u>=CH), 7.39 (1H, d, *J*=12.29 Hz, CH=C<u>H</u>), 8.43 (1H, d, *J*=6.71 Hz, D_2O exchang., CON<u>H</u>CH), 9.84 (1H, br s, D_2O exchang., CONHCO). ^{13}C-NMR (DMSO-d_6) δ: 14.50 (CH_3), 30.24 and 36.51 (C2+C5), 38.63 and 47.67 (C3+C4), 52.52 (C1), 62.90 (CH_2OH), 65.33 (CH_2OH), 67.34 (CH_2O), 98.46 (CO<u>C</u>H), 153.63 (NHCONH), 162.08 (EtO<u>C</u>H), 167.86 (NH<u>C</u>OCH). EI-MS *m*/*z* (%): 287 (1, $(M+1)^+$), 286 (3, M^+), 211 (9), 159 (37), 99 (100), 71 (62). *Anal.* Calcd for $C_{13}H_{22}N_2O_5$: C, 54.53; H, 7.74; N, 9.78. Found: C, 54.68; H, 7.67; N, 9.90.

(±)-1-[(1β,3α,4β)-3,4-bis(Hydroxymethyl)cyclopentyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (14) To a solution of (±)-**12** (0.22 g, 0.77 mmol) in dioxane (11 ml) was added 2 N H_2SO_4 (14 ml), and this mixture was refluxed for 30 min, allowed to cool, brought to pH 7 with 2 N NaOH, and concentrated to dryness. The residue was extracted with ethanol (3×30 ml), and concentration of the extracts left a residue that upon purification on silica gel with 5 : 1 EtOAc/MeOH as eluent afforded (±)-**14** (0.18 g, 97%) as a viscous paste. IR (film) γ_{max}: 3382, 3100, 2939, 1684, 1466, 1385, 1268 cm^{-1}. ^{1}H-NMR (DMSO-d_6), as previously reported.[18] ^{13}C-NMR (DMSO-d_6) δ: 30.15 and 34.58 (C2+C5), 38.08 and 44.39 (C3+C4), 58.56 (C1), 63.00 (CH_2O), 65.37 (CH_2O), 101.62 (<u>C</u>H=CH), 143.12 (CH=<u>C</u>H), 153.22 (NCONH), 163.21 (NH<u>C</u>OCH). EI-MS *m*/*z* (%): 241 (6, $(M+1)^+$), 240 (15, M^+), 192 (4), 151 (5), 113 (100). *Anal.* Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.11; H, 6.80; N, 11.60.

(±)-1-[(1β,3α,4β)-3,4-bis(Hydroxymethyl)cyclopentyl]-5-iodo-1,2,3,4-tetrahydropyrimidine-2,4-dione (6) A mixture of (±)-**14** (0.12 g, 0.5 mmol), dioxane (8 ml), I_2 (0.26 g, 1.02 mmol) and 0.75 N HNO_3 (0.68 ml) was refluxed for 2.5 h. After cooling, the solvents were removed under reduced pressure and the residue was chromatographed on silica gel with 50 : 1 EtOAc/MeOH as eluent, which afforded (±)-**6** (0.14 g, 78%) as a white solid that was washed with ether. mp 116—118 °C. IR (KBr) γ_{max}: 3424, 1684, 1457, 1302, 1026 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.42—1.68 (3H, m), 1.92—2.11 (2H, m), 2.21—2.41 (1H, m), 2.98—3.03 (2H, m, CH_2O), 3.08—3.12 (2H, m, CH_2O), 4.48—4.56 (3H, m, 1-H+2×OH (D_2O exchang.)), 8.15 (1H, s, CH=CI), 11.54 (1H, br s, D_2O exchang., CONHCO). ^{13}C-NMR (DMSO-d_6) δ: 30.01 and 34.55 (C2+C5), 38.03 and 44.31 (C3+C4), 59.61 (C1), 63.19 (CH_2O), 65.41 (CH_2O), 68.93 (CI), 147.51 (CI=<u>C</u>H), 150.90 (NCONH), 160.87 (NH<u>C</u>OCI). EI-MS *m*/*z* (%): 367 (53, $(M+1)^+$), 366 (96, M^+), 336 (46), 274 (37), 239 (100), 195 (99), 128 (14), 110 (98). *Anal.* Calcd for $C_{11}H_{15}IN_2O_4$: C, 36.08; H, 4.13; I, 34.66; N, 7.65. Found: C, 35.95; H, 4.30; I, 34.54; N, 7.76.

(±)-*N*-[(1β,2α,4β)-2,4-bis(Hydroxymethyl)cyclopentyl]-*N*′-(3-ethoxypropenoyl)urea (13) A solution of 3-ethoxypropenoyl isocyanate in benzene (14 ml, theoretically containing 5.79 mmol) was added dropwise under argon to a solution of (±)-**5** (0.55 g, 3.79 mmol) in dry DMF (18 ml) at −15 °C. A procedure analogous to that used to obtain (±)-**12** left a residue that upon purification by column chromatography afforded (±)-**13** (0.55 g, 51%) as a white solid. mp 113—115 °C. IR (KBr) γ_{max}: 3280, 3089, 2985, 1673, 1607, 1547, 1347, 1243, 1176, 1120 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.19—1.22 (1H, m), 1.24 (3H, t, *J*=7.02 Hz, CH_3), 1.52—1.57 (1H, m), 1.65—1.75 (2H, m), 1.79—1.84 (1H, m), 2.00—2.04 (1H, m), 3.27—3.36 (4H, m, 2×CH_2O), 3.93 (2H, c, *J*=7.13 Hz, C<u>H</u>$_2$CH$_3$), 3.99—4.01 (1H, m, 1-H), 4.60—4.66 (2H, m, D_2O exchang., 2×OH), 5.48 (1H, d, *J*=12.92 Hz, C<u>H</u>=CH), 7.54 (1H, d, *J*=12.31 Hz, CH=C<u>H</u>), 8.52 (1H, d, *J*=7.38 Hz, D_2O exchang., CON<u>H</u>CH), 9.99 (1H, br s, D_2O exchang., CONHCO). ^{13}C-NMR (DMSO-d_6) δ: 14.89 (CH_3), 36.62 and 36.88 (C3+C5), 43.04 and 43.36 (C2+C4), 49.74 (C1), 64.74 (CH_2OH), 65.00 (CH_2OH), 67.58 (CH_2O), 98.72 (CO<u>C</u>H), 153.72 (NHCONH), 162.30 (EtO<u>C</u>H), 167.92 (NHCOCH). EI-MS *m*/*z* (%): 287 (1, $(M+1)^+$), 286 (4, M^+), 257 (11), 144 (45), 99 (100), 71 (67). *Anal.* Calcd for $C_{13}H_{22}N_2O_5$: C, 54.53; H, 7.74; N, 9.78. Found: C, 54.45; H, 7.88; N, 9.66.

(±)-1-[(1β,2α,4β)-2,4-bis(Hydroxymethyl)cyclopentyl]-1,2,3,4-tetrahydropyrimidine-2,4-dione (7) Crude (±)-**7** was obtained from a solution of (±)-**13** (0.19 g, 0.66 mmol) in dioxane (8 ml) and 2 N H_2SO_4 (11 ml) by a procedure analogous to that described for the preparation of (±)-**14** from (±)-**12**, and upon chromatography on silica gel afforded pure (±)-**7** (0.15 g, 94%) as a white solid. mp 141—142 °C. IR (KBr) γ_{max}: 3326, 3042, 2881, 1683, 1465, 1393, 1268, 1198, 1080 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.45—1.56 (1H, m), 1.70—1.80 (3H, m), 1.94—2.02 (2H, m), 3.23—3.46 (4H, m, 2×CH_2O), 4.67—4.78 (3H, m, 1-H+2×OH (D_2O exchang.)), 5.56 (1H, d, *J*=7.92 Hz, C<u>H</u>=CH), 7.71 (1H, d, *J*=7.97 Hz, CH=C<u>H</u>), 11.18 (1H, br s, D_2O exchang., CONHCO). ^{13}C-NMR (DMSO-d_6) δ: 34.80 and 36.45 (C3+C5), 44.33 and 45.17 (C2+C4), 57.03 (C1), 66.16 (CH_2O), 66.44 (CH_2O), 102.97 (<u>C</u>H=CH), 144.31 (CH=<u>C</u>H), 153.89 (NCONH), 166.75 (NH<u>C</u>OCH). EI-MS *m*/*z* (%): 241 (8, $(M+1)^+$), 240 (19, M^+), 210

(17), 192 (66), 148 (6), 113 (100). *Anal.* Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.12; H, 6.79; N, 11.57.

(±)-1-[(1β,2α,4β)-2,4-bis(Hydroxymethyl)cyclopentyl]-5-iodo-1,2,3,4-tetrahydropyrimidine-2,4-dione (8) A mixture of (±)-**7** (0.14 g, 0.58 mmol), dioxane (9 ml), I2 (0.3 g, 1.18 mmol) and 0.75 N HNO_3 (0.8 ml) was refluxed for 3 h. After cooling, the solvents were removed under reduced pressure and the residue was chromatographed on silica gel with 50 : 1 EtOAc/MeOH as eluent, which afforded (±)-**8** (0.17 g, 85%) as a white solid. mp 80—82 °C. IR (KBr) γ_{max}: 3433, 3404, 2927, 1684, 1604, 1448, 1345, 1271, 1044 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.57—1.61 (1H, m), 1.74—1.78 (3H, m), 1.81—1.98 (2H, m), 3.33—3.43 (4H, m, 2×CH_2O), 4.64—4.72 (3H, m, 1-H+2×OH (D_2O exchang.)), 8.16 (1H, s, CH=CI), 11.57 (1H, br s, D_2O exchang., CONHCO). ^{13}C-NMR (DMSO-d_6) δ: 33.55 and 35.01 (C3+C5), 42.14 and 42.90 (C2+C4), 55.39 (C1), 64.36 (CH_2O), 64.48 (CH_2O), 69.11 (CI), 146.89 (CI=CH), 150.57 (NCONH), 160.75 (NHCOCI). EI-MS *m*/*z* (%): 367 (4, $(M+1)^+$), 366 (29, M^+), 336 (4), 239 (100), 195 (31). *Anal.* Calcd for $C_{11}H_{15}IN_2O_4$: C, 36.08; H, 4.13; I, 34.66; N, 7.65. Found: C, 36.17; H, 4.01; I, 34.52; N, 7.73.

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