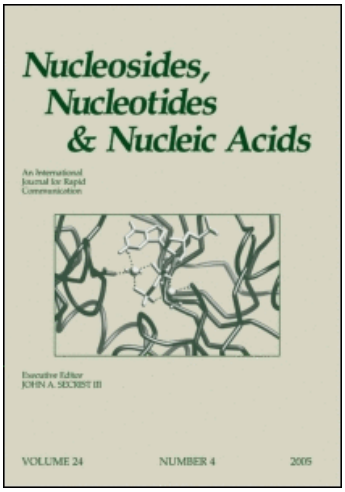

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Carbocyclic Analogues of 3',4'-Didehydro-2'-deoxyribofuranosyl-2,4(1*H*,3*H*)-pyrimidinediones

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CARBOCYCLIC ANALOGUES OF 3',4'-DIDEHYDRO-2'-DEOXYRIBOFURANOSYL-2,4(1*H*,3*H*)-PYRIMIDINEDIONES[1]

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ABSTRACT

A new method for obtaining carbocyclic analogues of 3',4'-didehydro-2,4(1*H*,3*H*)-pyrimidinedione nucleosides in good yields consists of the reaction of the carbocyclic 2,3'-anhydronucleosides with lithium chloride in dimethylformamide. Small amounts of the carbocyclic 2',3'-didehydro isomers are formed simultaneously. The carbocyclic 2,3'-anhydronucleosides were obtained by treating carbocyclic 5'-trityl derivatives with DAST.

INTRODUCTION

The discovery[2,3] of neplanocin A (**1**, P = 9-adenyl, X = Y = OH) stimulated much research on syntheses and biological evaluations of 4-cyclopentenyl analogues (**1**) of nucleosides. Much of this work has been reviewed by Marquez and Lim[4] and by Borthwick and Biggadike[5] (*cf.* Arita *et al.*,[6] Marquez and co-workers,[7,8] and references cited therein). Similarly, the synthesis of carbovir (**2**, P = 9-guanyl) by Vince and Hua,[9] and the discovery of its anti-HIV activity by Vince, Shannon, and co-workers[10] motivated investigations of 2-cyclopentenyl analogues of nucleosides (carbocyclic analogues of 2',3'-didehydronucleosides) (**2**, R = H). In contrast, only a few 3-cyclopentenyl analogues (**3**) of nucleosides (carbocyclic analogues of 3',4'-didehydronucleosides) have been reported. The latter analogues have been obtained either when an α,β-unsaturated aldehyde (**4**) could be formed[11] or as by-products formed by elimination of leaving groups from position 3 when a displacement reaction has been employed to introduce a new substituent. Béres *et al.*[12] reported the formation of a small amount of the trityl derivative (**7a**) of *C*-3',4'-didehydrothymidine (**8a**) in a mixture of fluoro derivatives when the 3α isomer (all-*cis*-*C*-tritylthymidine) of *C*-tritylthymidine (**5a**) was treated with diethylaminosulfur trifluoride (DAST); detritylation of the mixture furnished **8a** in 15% yield from **5a**. Béres *et al.*[13] also reported that **7a** was "a minor side product" of the reaction of triphenylphosphine iodide with the 3α-isomer of **5a**. Mixtures of 5-fluorouracil derivatives **2** and **3** (P = a 5-fluorouracil group, R = trityl, X = H) were identified

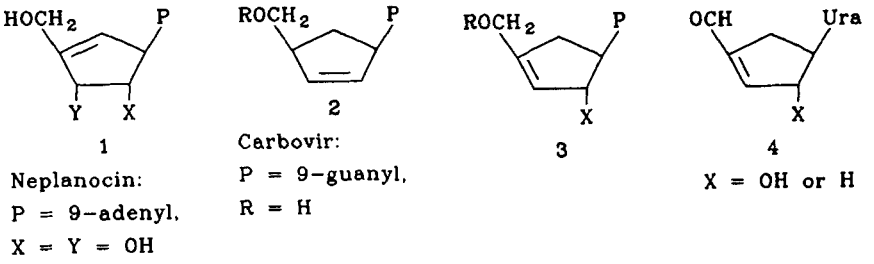

CHART I

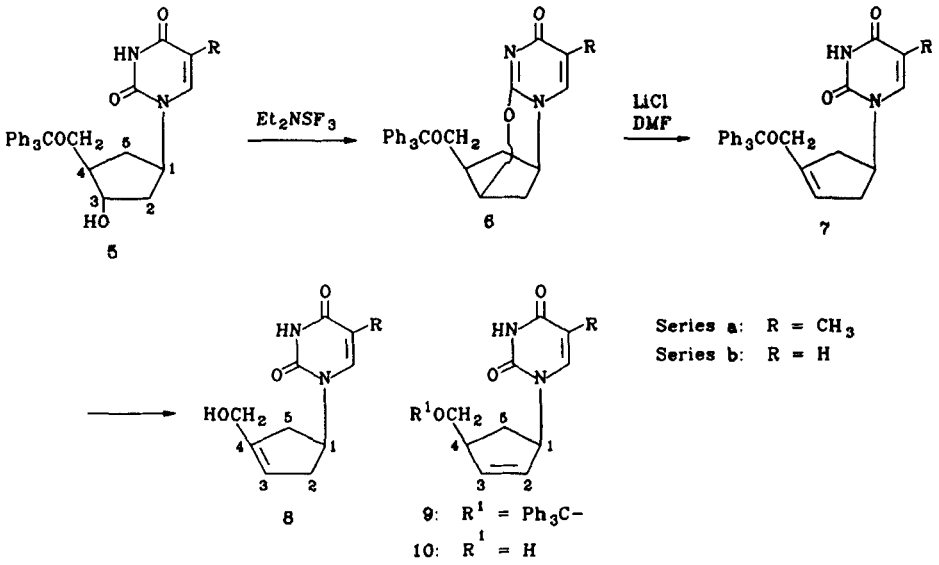

CHART II

by Hronowski and Szarek[14] as by-products in the formation of 3-halo derivatives from *C*-5-fluoro-3′α-mesyloxy-2′-deoxyuridine, and a mixture of the 5-fluoro analogues **2** and **3** with R = H was obtained by detritylation. A fluorothymidine analogue (**3**, P = thyminyl, X = F) was isolated by Highcock *et al.*[15] as a by-product (23% yield) of the reaction of DAST with a carbocyclic all-*cis*-thymidine having a silylated hydroxymethyl group and a 5β-fluoro substituent. The α,β-unsaturated aldehydes **4** were formed by an acid-catalyzed elimination of an ether group at position 3 from a cyclopentyluracil that has an acetal group at position 4.[11] Therefore, with the exception of the latter, special case, *C*-3′,4′-didehydropyrimidinedione nucleosides (**3**) have been obtained in low yields as by-products. We report herein a

different method that produces good yields of *C*-3',4'-didehydropyrimidinedione nucleosides (**3**) containing small amounts of the *C*-2',3'-didehydropyrimidinedione nucleosides (**2**).

CHEMISTRY AND BIOLOGICAL EVALUATIONS

The method is represented by structures **5-8**. The (±)-*C*-2,3'-anhydronucleosides (**6**) were isolated in yields of 80-85% by treating (±)-*C*-5'-tritylthymidine[16] (**5a**) or the deoxyuridine analogue (**5b**) with DAST in dichloromethane at -78 °C. After we had obtained **6** by this method, Baker and co-workers[17] reported the formation (at room temperature) of the corresponding true anhydronucleosides by this method. Prolonged heating of solutions of **6a** or **6b**, anhydrous lithium chloride, and DMF produced didehydro analogues in yields of 74-81%. Proton NMR spectra revealed that these products were (±)-*C*-3',4'-didehydro-5'-tritylthymidine (**7a**) or the 2'-deoxyuridine analogue (**7b**) containing small amounts of the (±)-*C*-2',3'-didehydro isomers (**9**); the ratios of **7**:**9** were 80-85:15-20. Detritylation of such mixtures of **7a** and **9a** with 25% acetic acid or 4-toluenesulfonic acid in 90% ethanol furnished (±)-*C*-3',4'-didehydrothymidine (**8a**), containing **10a**, in yields of 93% and 86%, respectively. Analysis of these mixtures either by HPLC or by proton NMR showed that they consisted of 83-85% **8a** and 15-17% **10a**. Recrystallization of a specimen of the mixture provided pure **8a** (HPLC analyses, greater than 99%). Similarly, detritylation of **7b** produced (±)-*C*-2'-deoxy-3',4'-didehydrouridine (**8b**) containing **10b**; the composition of the mixture was approximately the same as that of **8a-10a** mixtures. The course of the reaction of lithium chloride with **6b** was observed by maintaining a solution of lithium chloride, deuterated dimethyl formamide (DMF-D7), and **6b** at 100 °C in a capped NMR tube and recording spectra at intervals. Both **7b** and **9b** were observed, and the ratio of these two components remained approximately constant throughout the remainder of these determinations. This experiment indicated that **7b** and **9b** were being formed simultaneously. In similar experiments in which lithium bromide or lithium fluoride replaced lithium chloride in DMF-D_7, neither **7b** nor **9b** was observable by NMR after 9 days of heating at 100 °C. In another experiment, lithium iodide, DMF, and **6b** were heated under the conditions that produced **7b** when lithium chloride was the reagent, and aliquot portions were examined by thin-layer chromatography. After 7 days at 100 °C, **7b** was not detectable; but the addition of lithium chloride then produced observable **7b** within 24 hours, and the reaction proceeded approximately to completion within 8 days.

C-3',4'-Didehydrothymidine (**8a**) was not cytotoxic to CCRF-CEM cells or to L1210 mouse leukemia cells at concentrations of 10-40 μg/mL, and compound **8b** containing **10b** (83:15) was not cytotoxic to CCRF-CEM cells at 20 μg/mL. In antiviral tests against HSV-1 replicating in Vero cells, neither **8a** nor **8b** was inhibitory (IC_{50}>70 μg/mL or 208 μg/mL,

respectively). Similarly, in tests against human immunodeficiency virus (HIV-3B) in MT-2 or CEM cells, neither **8a** nor **8b** was active (IC_{50} > 100 μg/mL) or toxic to host cells (TC_{25} > 100 μg/mL).

EXPERIMENTAL SECTION

General Methods. Decomposition and melting temperatures (mp) were determined in capillary tubes heated in a Mel-Temp apparatus. Proton NMR spectra were recorded at 300.64 MHz with a Nicolet 300 NB NMR spectrometer. Tetramethylsilane was the internal standard; m = multiplet, s = singlet, d = doublet, t = triplet, bs = broad singlet, bd = broad doublet, dt = doublet of triplets. The apparent multiplicity of the signals, the number of the protons, and the assigned position of the protons (structures **5, 8-10**) are listed parenthetically with the chemical shifts. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane. ^{13}C-NMR spectra were determined at 75.602 MHz. Mass spectra were recorded on a Varian MAT 311A double-focusing mass spectrometer in the fast bombardment (FAB) mode. UV spectra were determined with a Perkin-Elmer Model Lambda 9 spectrometer, and absorption maxima are reported in nanometers. Solutions for ultraviolet spectral determinations were prepared by diluting a 5-mL aliquot of a water or ethanol solution to 50 mL with 0.1 *N* hydrochloric acid, phosphate buffer (pH 7), or 0.1 *N* sodium hydroxide. Absorption maxima of these solutions are reported as being determined at pH 1, 7, or 13, respectively. High pressure liquid chromatography (HPLC) was performed with a Hewlett-Packard 1084B liquid chromatograph, equipped with a variable wavelength detector set at 280nm, and automatic injector. Two columns were employed in the determinations. Column A was Waters μBondapak C_{18} column; particle size 10μ, pore size 125Å. Column B was an IMB Optima II column; particle size 5μ, pore size 100Å. Column chromatography was performed on silica gel 60 (230-400 mesh).

(±)-(1α,3β,4α)-1-[3-Hydroxy-4-[(triphenylmethyl)oxy]cyclopentyl-2,4(1*H*,3*H*)-pyrimidinedione (5b). A solution (protected from atmospheric moisture) of *C*-2'-deoxyuridine[18] (830 mg, 3.67 mmol), triphenylmethyl chloride (1.33 g, 4.77 mmol), and dry pyridine (41 mL) was heated at 100 °C for 18 hr. and then concentrated to dryness. Three portions of methanol were evaporated from the residue; crystals formed when a hot methanol (15 mL) solution of the residue was cooled. The mixture was refrigerated, and the precipitate was collected by filtration, washed with cold ethanol, and dried *in vacuo* at 78 °C: weight, 730 mg; mp, 196-199 °C. The residue obtained by concentration of the filtrate and washings was dissolved in 5:1 chloroform-ethyl acetate and chromatographed on a column of silica gel (30 g). After triphenylmethanol had been eluted by the same solvent, the product was eluted with 95:5 chloroform-methanol. Concentration of product-containing fractions (identified by TLC) afforded white crystals: weight, 587 mg (total yield, 76%); mp, 198-200 °C. *Anal.* calcd. for $C_{29}H_{28}N_2O_4$: C, 74.33; H, 6.02; N, 5.98. Found: C, 74.00; H, 6.20; N, 5.96.

Carbocyclic Analogue (6a) of 2,3'-Anhydro-5'-*O*-tritylthymidine. This compound was synthesized previously by a different two-step method.[16] The following procedure illustrates the DAST method and gives a higher yield from **5a**. A solution of **5a**[16] (225 mg, 0.47 mmol) in dichloromethane (4 mL, dried over 4A molecular sieves) was stirred under an anhydrous nitrogen atmosphere and chilled to -78 °C. A solution of diethylamino- sulfur trifluoride (DAST, 81 mg, 0.5 mmol) in dried dichloromethane (4 mL) was added dropwise to the solution of **5a**, and the resulting reaction mixture was stirred at -78 °C for 0.5 h. The mixture was allowed to warm to room temperature, water (5 mL) was added, and the mixture was stirred vigorously for several minutes. The dichloromethane layer was separated, washed with sodium bicarbonate solution, dried over $MgSO_4$, and concentrated under reduced pressure to a foam (197 mg). A solution of the crude product in chloroform-methanol (95:5) was poured onto a column of silica gel (30 g), and the column was eluted with the same solvent. Fractions containing **6a** (determined by TLC) were combined and concentrated under reduced pressure to a white solid: yield 175 mg (81%); mp 234-237 °C dec. (capillary inserted at 100 °C); MS *m/z* 465 (M + H); ^{1}H NMR (DMSO-D_6) δ 1.52 m and 2.10 m (CH_2, position 5), 1.75 s (CH_3), 2.15 m and 2.24 m (CH_2, position 2), 2.55 m (CH, position 4), 2.99 m and 3.19 t (CH_2OCPh_3), 4.38 bs (CH, position 1), 5.17 bs (CH, position 3), 7.16-7.46 m (phenyl and pyrimidine CH).

Carbocyclic Analogue (6b) of 2,3'-Anhydro-5'-*O*-trityl-2'-deoxyuridine. Compound **5b** was treated with DAST according to the procedure described for the preparation of **6a**, and the crude product was subjected to column chromatography as described for the purification of **6a**. The eluted **6b** was either recrystallized from ethanol or chromatographed again on silica gel with chloroform-ethyl acetate (5:1) as the eluting solvent: white solid (84% yield); mp 222-225 °C dec (inserted at 100 °C); MS *m/z* 451 (M + H), 243 (Ph_3C^+); UV λ_{max} in nm (ϵ) 257 (7200) at pH 1, 255 (7300) at pH 7, and 255 (7200) at pH 13. *Anal.* calcd. for $C_{29}H_{26}N_2O_3 \cdot 3/4C_2H_5OH$: C, 75.52; H, 6.34; N, 5.78. Found: C, 75.63; H, 6.08; N, 6.16.

(±)-5-Methyl-1-[[4-[(triphenylmethyl)oxy]methyl]-3-cyclopentenyl]-2,4(1*H*,3*H*)-pyrimidinedione (7a). A solution (protected from atmospheric moisture with a tube of Drierite) of 310 mg (0.67 mmol) of **6a**, 550 mg (13 mmol) of dry lithium chloride, and 30 mL of dry dimethylformamide was heated at 100 °C for 8 days and then concentrated to dryness *in vacuo*. A solution of the residue in 9:1 chloroform-methanol was filtered, and the filtrate, together with the washings, was concentrated *in vacuo* to a syrup. A solution of the syrup in 95:5 chloroform-methanol was poured onto a column of silica gel (25 g), and the column was eluted with the same solvent. Product-containing fractions (identified by TLC) were combined, filtered, and concentrated to a syrup; yield, 230 mg (74%). The residue was triturated with ethanol: white crystals; MS *m/z* 465 (M + H), 243 (Ph_3C^+); significant ^{1}H-NMR signals from **7a** and ethanol (DMSO-D_6) δ 3.58 m (CH_2OCPh_3), 5.15 heptuplet (CH at

position 1), 5.78 m (CH at position 3), 1.06 t and 3.44 m (C_2H_5OH). The presence of a small amount of **9a** was shown by weak ^{1}H-NMR signals at δ 2.82 m, 5.45 m, 5.75 dt, and 6.16 dt arising from CH at positions 4, 1, 2, and 3, respectively, and 3.45 m (CH_2OCPh_3); ^{1}H-NMR **7a**:**9a**, 82-85%:15-18%. *Anal.* calcd. for $C_{30}H_{28}N_2O_3 \cdot 3/4C_2H_5OH$: C, 75.80; H, 6.56; N, 5.61. Found: C, 75.74; H, 6.51; N, 5.89.

(±)-1-[4-[[Triphenylmethyl)oxy]methyl]-3-cyclopentenyl]-2,4(1*H*,3*H*)-pyrimidinedione (7b). A mixture (protected from atmospheric moisture with a tube of Drierite) composed of **6b** (730 mg, 1.62 mmol), lithium chloride (1.40 g, 33.1 mmol), and DMF (50 mL) was heated at 110 °C for 48 h and then concentrated to dryness *in vacuo*. Several portions of methanol were evaporated from the gummy residue. The purified product was obtained by column chromatography on silica gel as described for the purification of **7a**. Recrystallization of the resulting solid from ethanol, and drying the crystalline product at 78 °C *in vacuo*: yield, 590 mg (81%); MS *m/z* 451 (M + H), 243 (Ph_3C^+); ^{1}H NMR (Me_2SO-D_6) δ 2.40 m and 2.76 m ($2CH_2$, positions 5 and 2), 3.59 bs (CH_2OH), 5.13 heptuplet (CH, position 1), 5.58 dd (5-pyrimidine CH), 5.78 bs (CH, position 3), 7.2-7.48 m (Ph_3C and 6-pyrimidine CH of **7b** and **9b**), 11.23 bs (NH of **7b** and **9b**); weak ^{1}H-NMR signals from **9b** at δ 1.22 m (1H, CH_2 at position 5), 2.98 m (2H, CH_2 and CH at positions 5 and 4), 3.13 m and 3.58 m (CH_2OH), 5.31 m (5-pyrimidine CH), 5.43 m (CH at position 1), 5.76 dt (CH at position 2), 6.18 dt (CH at position 3), 7.2-7.48 m and 11.23 bs as listed above; ^{1}H-NMR **7b**:**9b**, 80-82%:18-20%. *Anal.* calcd. for $C_{29}H_{26}N_2O_3 \cdot 1/4C_2H_5OH$: C, 76.68; H, 6.00; N, 6.06. Found: C, 76.33; H, 5.87; N, 6.32.

A mixture that was similar except that lithium iodide (10 equivalents) replaced lithium chloride was heated at 100 °C. Aliquot portions were examined by TLC after 1, 2, 4, 5, and 7 days of heating; **7b** or **9b** was not observable. Lithium chloride (20 equivalents) was added and heating was continued at 100 °C; TLC of an aliquot removed after 24 h showed that some **7b** (or **7b** + **9b**) had formed. The product isolated 8 days after the addition of lithium chloride was identified as **7b** (or **7b** + **9b**) by TLC and the mass spectral peak at 451 (M + H).

(±)-5-Methyl-1-[4-(hydroxymethyl)-3-cyclopentenyl]-2,4(1*H*,3*H*)-pyrimidinedione (8a). A mixture of 90 mg of **7a** and 10 mL of 25% acetic acid was heated under reflux for 0.5 h and then concentrated *in vacuo* to a paste. A solution of the residue in 9:1 chloroform-methanol was poured onto a column of silica gel (25 g, 230-400 mesh), the column was eluted with the same solvent, and product-containing fractions (collected after triphenylmethanol had been eluted) were concentrated to a white crystalline solid: yield, 40 mg (93%); mp 185-190 °C; MS *m/z* 223 (M + H), 127 (P + 2H); HPLC (column A; 75:25 H_2O-MeOH, isocratic; order of elution) 83% **8a**, 17% **10a**; ^{1}H-NMR (Me_2SO-D_6) analysis, **8a**:**10a**, 83%:17%; δ of **10a** 1.35 m and 2.49 m (CH_2 at position 5), 1.75 s (CH_3), 2.79 m (CH at position 4), 3.45 m (CH_2OH), 4.73 t (CH_2OH), 5.5 m (CH at position 1, overlapped with CH at position 4 of **8a**),

5.69 dt (CH at position 2), 6.09 dt (CH at position 3), 7.34 s (pyrimidine CH) 11.20 s (NH); ^{1}H-NMR of **8a**, below. A similar specimen was recrystallized from ethanol: mp 193-196 °C (inserted at 100 °C, 3°/min); HPLC (column A; 75:25 H_2O-MeOH, isocratic; order of elution) 99.3% **8a**, 0.7% **10a**; HPLC (column B; 9:1 H_2O-CH_3CN, isocratic; order of elution) 0.5% **10a**, 99.5% **8a**; UV λ_{max} in nm (ϵ) 274 (10 900) at pH 1 or 7, 272 (8500) at pH 13; ^{1}H NMR (Me_2SO-D_6) δ 1.76 s (CH_3), 2.38 m and 2.71 m ($2CH_2$ at positions 2 and 5), 3.99 bs (CH_2OH), 4.81 t (OH), 5.13 heptuplet (CH at position 1), 5.55 bs (CH at position 3), 7.27 s (pyrimidine CH), 11.20 s (NH); ^{13}C-NMR (Me_2SO-D_6, 75.602 MHz) δ 12.096 (CH_3), 38.061 and 38.127 (C2 and C5), 53.145 (C1), 59.536 (CH_2OH), 109.311 (pyrimidine C5), 121.514 (C3), 137.252 (pyrimidine C6), 143.754 (C4), 150.557 (pyrimidine C2), 163.606 (pyrimidine C4). *Anal.* calcd. for $C_{11}H_{14}N_2O_3 \cdot 1/4C_2H_5OH$: C, 59.08; H, 6.68; N, 11.99. Found: C, 59.38; H, 6.83; N, 12.19.

A mixture of compounds **8a** and **10a** was obtained also by heating a solution of **7a**, 4-toluenesulfonic acid, and 90% ethanol under reflux during 16 hr: 86% yield of **8a** and **10a**; HPLC (column A; 75:25 H_2O—MeOH, isocratic) 81.4% **8a**, 18.6% **10a**; ^{1}H-NMR spectrum identical with that of the mixture obtained by detritylation with 25% acetic acid.

(±)-1-[4-(Hydroxymethyl)-3-cyclopentenyl]-2,4(1*H*,3*H*)-pyrimidinedione (8b). A stirred mixture of **7b** (400 mg, 0.89 mmol), 4-toluenesulfonic acid (100 mg), and 90% ethanol (40 mL) was heated at 60 °C during 5 h. The mixture became homogeneous during this time, stirring was continued for 18 h, and then the mixture was concentrated to dryness *in vacuo*. A white solid was isolated by the method described for **8a**, triturated with ethyl acetate, and dried at 78 °C *in vacuo*; mp 135-140 °C. A mixture of the solid and 9 mL of hot acetonitrile was filtered to remove a small amount of white solid. The filtrate (plus washings) was concentrated *in vacuo* to a white solid that was dried at 78 °C *in vacuo*: yield of **8b** containing a small amount of **10b**, 106 mg (57%);[19] mp 140-145 °C (inserted at 120 °C, 3 °C/min, softening at 135-140 °C); MS *m/z* 209 (M + H), 113 (P + 2H); HPLC (column A; 75:25 H_2O—MeOH, isocratic) 83% **8b**, 15% **10b**; UV λ_{max} in nm (ϵ) 269 (10 800) at pH 1 or pH 7, and 267 (8000) at pH 13; ^{1}H NMR (Me_2SO-D_6) δ 1.35 dt and 2.52 m (CH_2 at position 5 of **10b**), 2.37 m and 2.73 m ($2CH_2$ at positions 2 and 5 of **8b**), 2.78 m (CH at position 4 of **10b**), 3.43 m (CH_2OH of **10b**), 3.99 bd (CH_2OH of **8b**), 4.72 t (CH_2OH of **10b**), 4.82 t (CH_2OH of **8b**), 5.12 heptuplet (CH at position 1 of **8b**), 5.49 m (CH at position 1 of **10b**), 5.52-5.64 m (CH at position 3 of **8b** + 5-pyrimidine CH of **8b** and **10b**), 5.68 dt (CH at position 3 of **10b**), 6.09 dt (CH at position 2 of **10b**), 7.40 d (6-pyrimidine CH of **8b**), 7.47 d (6-pyrimidine CH of **10b**), 11.22 bs (NH of **8b** and **10b**); ^{1}H-NMR **8b**:**10b**, 84-86%: 14-16%. *Anal.* calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.49: H, 5.84; N, 13.39.

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REFERENCES AND NOTES

1. The prefix *C* should be read as carbocyclic analogue of. When these analogues are named as nucleosides, the primed numbering system of the true nucleosides is used to designate positions on the cyclopentyl ring. When they are named as cyclopentanes or cyclopentenes, the numbering of positions is that shown on structures **5** and **8**.
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19. In two subsequent larger-scale runs, yields were 70%.

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