Carbocyclic 5'-Norcytidine (5'-Norcarbodine)

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A preparation of (1'*R*,2'*S*,3'*R*,4'*S*)-1-(2',3',4'-trihydroxycyclopent-1'-yl)-1*H*-cytosine (5'-norcarbodine, **3**) has formally been achieved in 2 steps from (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**4**) and cytosine. The L-like enantiomer of **3** (that is, **6**) is also reported using the enantiomer of **4** (that is, **7**). In evaluating **3** and **6** for antiviral potential against a number of viruses, compound **3** was found to have activity towards Epstein-Barr virus (EBV).

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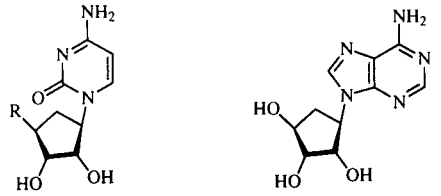
The carbocyclic nucleosides have provided the basis for a fruitful search for antiviral agents [3]. Of this series of compounds, carbocyclic cytidine (carbodine, **1**) has shown a broad range of activity against a number of DNA, (+)-RNA, (-)-RNA and (±)-RNA viruses [4]. Because of a similar antiviral potential for 5'-noraristeromycin (**2**) [5], the truncated 5'-norcarbodine (**3**) was sought to extend the usefulness of pyrimidine based carbocyclic nucleosides into the 5'-nor series [6].



1: R = CH_2OH
3: R = OH

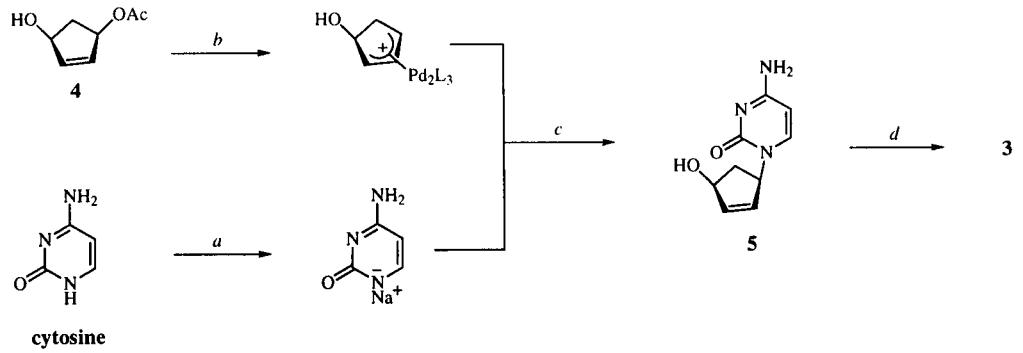
2

Figure 1.

The synthesis of **3** followed our standard [7] route to the 5'-nor carbocyclic nucleosides but required a separate generation of the allylic palladium(II) complex of (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**4**) [8] and the anion of cytosine [9] (Scheme). Conducting this coupling in a mixture of tetrahydrofuran and dimethylformamide at 60 °C provided the 2',3'-dideoxy derivative (1*R*,4*S*)-1-(4-hydroxy-2-cyclopenten-1-yl)-1*H*-cytosine (**5**). Glycosylation of **5** led to the desired (1'*R*,2'*S*,3'*R*,4'*S*)-1-(2',3',4'-trihydroxycyclopent-1'-yl)-1*H*-cytosine (**3**). Confirmation that 2',3'-dihydroxylation had occurred on the α-face of the cyclopentyl substituent was accomplished by comparing the nmr spectral properties of **3** with related analogs [5]. The enantiomeric **6** was prepared in an analogous fashion to **3** beginning with (-)-(1*S*,4*R*)-4-hydroxy-2-cyclopenten-1-yl acetate (**7**) [10], the enantiomer of **4**.

Compounds **3** and **6** were found to be inactive against herpes simplex 1, herpes simplex 2, varicella zoster virus, human cytomegalovirus, and (for **3**) hepatitis B. Moderate activity was found for **3** towards vaccinia virus and vesicular stomatitis virus. Interestingly, however, **3** was quite effective in inhibiting Epstein Barr virus (EBV) in both the VCA Elisa (EC_{50} 0.21, μg/mL) and DNA hybridization (EC_{50} 4.3 μg/mL) with no accompanying toxicity toward the host Daudi cells. On the other hand, **6** was tenfold less potent towards EBV but was very toxic to the host cell line (IC_{50} in cell proliferation 5.6 μg/mL). The effect of **3** on EBV is particularly noteworthy in light of the serious clinical effects of EBV [11], which must be tolerated without the availability of effective agents for

Scheme



4

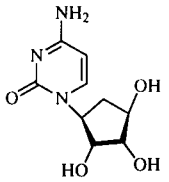
cytosine

5

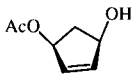
3

Reaction conditions: *a*, sodium hydride in dimethylformamide; *b*, $Pd_2(dba)_3CHCl_3$; *c*, mix at 60 °C; *d*, OsO_4, 60% aq. 4-methylmorpholine *N*-oxide.

treatment that do not also present the patient with undesirable side effects. A recent paper [12] suggests the L-nucleosides may offer hope for safe treatment of EBV. Compound **3**, on the other hand, can be viewed as a D-like derivative.



6



7

Figure 2.

EXPERIMENTAL

General.

Melting points were recorded on a Meltemp II melting point apparatus and are uncorrected. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ^1H and ^{13}C spectra were recorded on a Bruker AC 250 spectrometer (operated at 250 and 62.5 MHz, respectively) all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. The spin multiplicities are indicated by the symbols d (doublet), t (triplet), m (multiplet) and br (broad). Optical rotations were measured on a JASCO DIP-360 polarimeter. Reactions were monitored by thin-layer chromatography (tlc) using 0.25 mm Whatman Diamond silica gel 60-F_{254} precoated plates with visualization by irradiation with a Mineralight UVGL-25 lamp. Column chromatography was performed on Whatman silica, 230-400 mesh, 60 Å and elution with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C nmr) homogeneous materials. Abbreviations: $Pd_2(dba)_3$, tris(dibenzylideneacetone)-palladium: dppp, 1,3-bis(diphenyl)phosphinopropane.

(1*R*,4*S*)-1-(4-Hydroxy-2-cyclopenten-1-yl)-1*H*-cytosine (**5**).

To a solution of cytosine (0.98 g, 8.8 mmoles) in dry dimethylformamide (20 ml) was added sodium hydride (0.23 g, 95% dry powder, 8.8 mmoles) and the reaction mixture stirred at 70 °C for 1 hour. To this suspension was added, with the aid of a syringe, a solution of the complex generated by the addition of $Pd_2(dba)_3$ (0.182 g. 0.32 mmole) and dppp (0.18 g, 0.44 mmole) to (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**4**) [8] (1.136 g, 8 mmoles) in dry tetrahydrofuran (20 ml) with stirring at 55 °C for fifteen minutes. This mixture was stirred for two days at 60 °C. The volatiles were removed by rotary evaporation. The residue was then purified *via* column chromatography eluting with dichloromethane-methanol (4:1). The fractions containing product were combined and the solvent removed under reduced pressure to give 1.21 g (71%) of **5** as a white solid, which was recrystallized from dichloromethane-methanol (4:1), mp >200 °C (dec); ^1H nmr (hexadeuteriodimethyl sulfoxide) δ 1.30 (dt, 1H, methylene), 2.69 (dt, 1H, methylene), 4.62 (m, 1H, H-1'), 5.20 (br, 1H, hydroxyl), 5.45 (m, 1H, H-4'), 5.75 (dd, 1H, H-2'), 6.09 (dd, 1H, H-3'), 6.11 (d, 1H, pyrirnidine), 7.15 (br, 2H, amino), 7.41 (d, 1H, pyrimidine); ^{13}C nmr (hexadeuteriodimethyl sulfoxide) δ 38.7, 57.7, 73.8, 93.7, 129.0, 132.8, 142.6, 156.3, 165.0.

Anal. Calcd. for $C_9H_{11}N_3O_2 \cdot 0.5\ H_2O$: C, 55.46; H, 5.98; N, 20.78. Found: C, 55.30; H, 5.97; N, 20.45.

(1'*R*,2'*S*,3'*R*,4'*S*)-1-(2',3',4'-Trihydroxycyclopent-1'-yl)-1*H*-cytosine (**3**).

To a solution of **5** (1.0 g, 7.19 mmoles) in tetrahydrofuran-water (20 mL 10:1) was added osmium tetroxide (0.05 g) and 4-methylmorpholine *N*-oxide (1.5 ml). The mixture was stirred at room temperature for 24 hours until tlc (ethyl acetate-methanol, 4:1) showed no remaining starting material. The solvent was evaporated with the aid of a rotary evaporator and the residue purified *via* column chromatography (ethyl acetate-methanol, 4:1). Fractions containing product were combined and evaporated to afford 0.83 g (67%) of **3** as a white solid, which was recrystallized from ethyl acetate-methanol (4:1), mp 215 °C; $[\alpha]_D^{23}$ + 3.41 °C (*c* 0.70, methanol); ^1H nmr (hexadeuteriodimethyl sulfoxide) δ 1.41 (dt, 1H, methylene), 1.86 (m, 1H, methylene), 3.66 (br, 1H, hydroxyl), 3.78 (br, 1H, hydroxyl), 4.20 (br, 1H, hydroxyl), 4.57 (dd, 1H, H-1'), 4.60 (dd, 1H, H-4'), 4.76 (m, 1H, H-2'), 5.21 (m, 1H, H-3'), 5.75 (d, 1H, pyrirnidine), 7.06 (br, 2H, amino), 7.63 (d, 1H, pyrimidine); ^{13}C nmr (hexadeuteriodimethyl sulfoxide) δ 35.89, 61.35, 73.48, 75.52, 76.73, 93.88, 144.02, 156.01, 165.20.

Anal. Calcd. for $C_9H_{13}N_3O_4 \cdot 0.33\ H_2O$: C, 46.36; H, 5.90; N, 18.02. Found: C, 46.28; H, 6.13; N, 18.34.

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