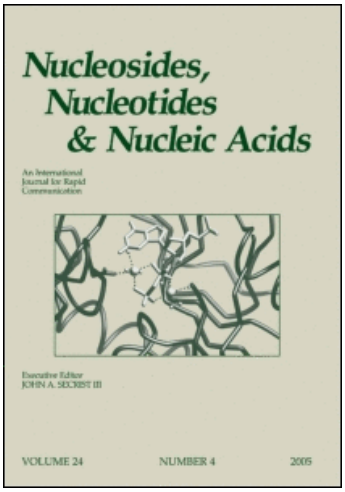

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CARBOCYCLIC 5'-NORURIDINE

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Dedicated to the memory of Dr. Gertrude B. Elion

ABSTRACT

A convenient preparation of (1'*R*,2'*S*,3'*R*,4'*S*)-1-(2',3',4'-trihydroxycyclopent-1'-yl)-*1H*-uracil (carbocyclic 5'-noruridine, **1**) is described in 2 steps from the palladium complex of (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**3**) and the sodium salt of uracil (**2**). Compound **1** was sought as a previously unknown member of the series of carbocyclic 5'-nor nucleosides needed as moieties for new oligomers. With **1** available, its antiviral properties and those of its enantiomer (**5**) are reported with **5** showing promising activity towards Epstein-Barr virus.

For some time our laboratory has been interested in carbocyclic nucleosides lacking the 5'-methylene unit (designated as the 5'-nor series).[3] In addition to seeking these derivatives for their potential antiviral properties,[4] it has been a long intended desire to include these monomers in homo oligomers as well as in oligomers that also contain natural and carbocyclic nucleosides possessing the 5'-center.[5] Missing from the pyrimidine toolbox[6] is carbocyclic 5'-noruridine (**1**). A facile synthesis of this derivative and the results of its effect on various viruses are presented here.

In considering the synthesis of **1**, the standard isocyanate approach[7] using an appropriately constructed cyclopentylamine was considered too lengthy and tedious for the purpose of this research. Thus, the palladium mediated coupling process with a cyclopentyl allylic acetate that was utilized for preparing the thymine derivative[6] was evaluated. This procedure[6] required protection (benzoyl) of the thymine N-3 before coupling at the desired N-1 could be accomplished. However, numerous attempts (for

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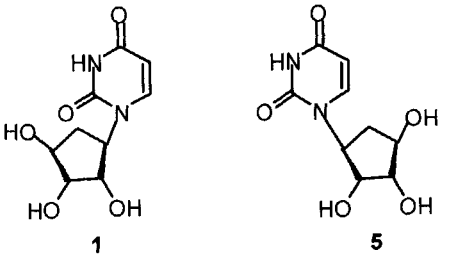
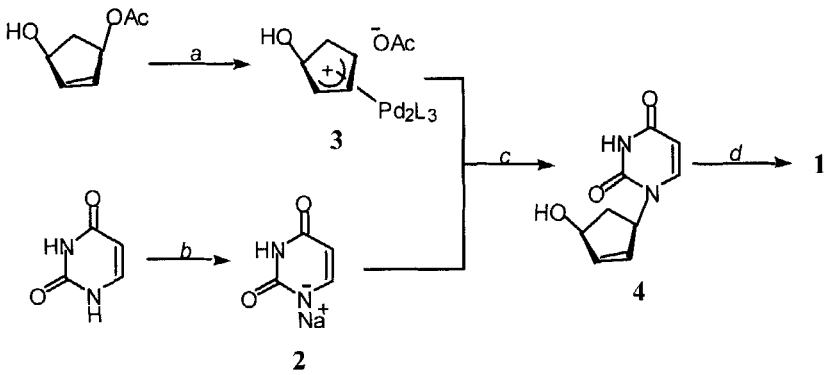


FIGURE 1

example, see reference 8) with 3-benzoyluracil failed. Surprisingly, conversion of uracil itself to its sodium salt **2**[9] led to successful coupling with the palladium complex of (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**3**)[10] to give **4**.[11] Glycolization of **4** provided the target compound **1**.[12] Replacing **3** with its enantiomeric complex (available from (-)-(1*S*,4*R*)-4-hydroxy-2-cyclopenten-1-yl acetate)[4b] presented the optical antipode of **1** (**5**).



Reaction conditions: *a*, $Pd_2(dba)_3 \cdot CHCl_3$, dppp, 55 °C, 15 min; *b*, NaH in DMF, 70 °C, 1 h ; *c*, mix at 60 °C; *d*, OsO_4, 60% aq. 4-methylmorpholine *N*-oxide

SCHEME 1

Compounds **1** and **5** were found to be inactive against herpes simplex 1, herpes simplex 2, varicella zoster virus, human cytomegalovirus, hepatitis B virus, vaccinia virus and vesicular stomatitis virus and (for **1**) Epstein-Barr virus (EBV). Interestingly, however, **5** was effective in inhibiting EBV in the VCA Elisa assay (EC_{50} 0.51 μg/mL;

EC_{50} for acyclovir 0.2 μg/mL) but was very toxic to the host (Daudi) cell line (IC_{50} in cell proliferation 12 μg/mL). The effect of **5** is consistent with a recent report[13] suggesting the L-nucleosides as meaningful anti-EBV candidates if **5** is viewed as a L-like derivative.

Experimental. 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). *J* values are expressed in Hz. 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)dipalladium; dppp, 1,3-*bis*(diphenyl)phosphinopropane

(1'*R*,2'*S*,3'*R*,4'*S*)-1-(2',3',4'-Trihydroxycyclopent-1'-yl)-*1H*-uracil (1). To a suspension of uracil (0.9 g, 8 mmol) in dry DMF (25 mL) was added NaH (0.2 g, 95% dry powder, 8 mmol) and the reaction mixture stirred at 70 C for 1 h. To this suspension was added, with the aid of a syringe, a solution of the complex generated by the addition of $Pd_2(dba)_3 \bullet CHCl_3$ (0.182 g. 0.32 mmol) and dppp (0.18 g, 0.44 mmol) to (+)-(1*R*,4*S*)-4-hydroxy-2-cyclopenten-1-yl acetate (**3**)[6] (1.14 g, 8 mmol) in dry THF (25 mL) with stirring at 55 C for 15 min. The resulting mixture was stirred at 60 C for 2 days. The reaction was monitored by TLC and when over, the volatiles were removed by rotary evaporation. The residue was then purified via column chromatography eluting with CH_2Cl_2/MeOH (1:9). The fractions containing product were combined and the solvent removed under reduced pressure to give 2 g (67%) of (1'*R*,4'*S*)-1-(4'-hydroxy-2'-cyclopenten-1'-yl)-*1H*-uracil (**4**) as a white solid, which was recrystallized from CH_2Cl_2/MeOH (4:1), mp 192 C; ^1H NMR (DMSO-d_6) δ 1.75 (dt, 1H, CH_2), 1.90 (dt, 1H, CH_2), 4.90 (m, 1H, H-1'), 5.10 (br, 1H, OH), 5.55 (m, 1H, H-4'), 5.65 (dd, 1H, H-2', *J*=5, 5, 12.5), 5.82 (dd, 1H, H-3', *J*=5, 5, 12), 6.10 (d, 1H, pyrimidine), 7.2 (d, 1H, pyrimidine),

11.3 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 38.5, 60.5, 74.3, 101.68, 131.21, 141.0, 141.5, 151.1, 163.4.

To a solution of **4** (0.45 g, 2.3 mmol) in THF/H_2O (20 mL, 10:1) was added OsO_4 (0.05 g) and 4-methylmorpholine N-oxide (1 mL). The mixture was stirred at room temperature for 24 h until TLC (CH_2Cl_2/MeOH, 4:1) showed no remaining starting material. The solvent was evaporated under reduced pressure and the residue purified via column chromatography (CH_2Cl_2/MeOH, 4:1). Fractions containing product were combined and evaporated to afford 0.31 g (59%) of **1** as a white solid, which was recrystallized from EtOAc/MeOH (4:1), mp 186 C (dec.); $[\alpha]^{23}_D$ –58.34° (*c* 0.40, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.52 (dt, 1H, CH_2), 2.05 (dt, 1H, CH_2), 3.52 (br, 1H, OH), 3.82 (br, 1H, OH), 4.62 (br, 1H, OH), 4.80 (m, 1H, H-1'), 5.4 (m, 1H, H-4'), 5.52 (dd, 1H, H-2', *J*=5, 5, 12), 5.63 (dd, 1H, H-3', *J*=5, 5, 15), 6.21 (d, 1H, pyrimidine), 7.09 (d, 1H, pyrimidine), 11.12 (br, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 36.82, 60.38, 73.58, 76.12, 77.83, 102.90, 135.38, 152.12, 162.0. Calcd. for $C_9H_{12}N_2O_5$•0.66 H_2O: C, 45.02; H, 5.59; N, 11.67. Found: C, 44.94; H, 5.25; N, 11.58.

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REFERENCES

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3. For a leading reference see Hegde, V.R.; Seley, K.L.; Schneller, S.W.; Elder, T.J.J. *J. Org. Chem.* **1998**, *63*, 7092-7094.
4. For example, see (a) Siddiqi, S.M.; Chen, X.; Schneller, S.W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551-554. (b) Seley, K.L; Schneller, S.W.; Korba, B. *Nucleosides Nucleotides* **1997**, *16*, 2095-2099.

5. Koga, M.; Abe, K.; Ozaki, S.; Schneller, S.W. *Nucleic Acids Symposium Series No. 31* **1994**, 65-66.

6. Hegde, V.R.; Seley, K.L.; Chen, X.; Schneller, S.W. *Nucleosides Nucleotides* **1999**, *18*, 1905-1910.

7. Shealy, Y.F.; O'Dell, C.A. *J. Heterocyclic Chem.* **1976**, *13*, 1015-1020.

8. Kapeller, H.; Marschner, C.; Weißenbacher, M.; Griengl, H. *Tetrahedron* **1998**, *54*, 1439-1456.

9. Liotta, F.; Unelius, R.; Kozak, J.; Norin, T. *Acta Chem. Scand.* **1992**, *46*, 686-688.

10. Siddiqi, S..M.; Chen, X.; Schneller, S.W. *Nucleosides Nucleotides* **1993**, *12*, 267-278.

11. Confirmation that coupling had occurred at the N-1 position was accomplished by comparing the pyrimidine portion of the ^{13}C NMR spectrum of **4** with a related derivative reported in reference 9.

12. To ensure that the 2',3'-diol function of **1** was in the desired configuration, the cyclopentyl portion of its ^{13}C NMR spectrum was compared with that of similar 5'-nor carbocyclic nucleosides prepared using OsO_4 and 4-methylmorpholine N-oxide.[14]

13. Lin, J.-S.; Kira, T.; Gullen, E.; Choi, Y.; Qu, F.; Chu, C.K.; Cheng, Y.-C. *J. Med. Chem.* **1999**, *42*, 2212-2217.

14. Hegde, V.R.; Seley, K.L.; Schneller, S.W.; Elder, T.J.J. *J. Org. Chem.* **1998**, *63*, 7092-7094.