(10) C. M. Woodard, D. S. Brown, J. D. Lee, and A. G. Massey, *J. Organomet. Chem.*, **121**, 333 (1976).
(11) J. D. Lee and M. W. R. Bryant, *Acta Crystallogr., Sect. B*, **26**, 1729 (1970).
(12) S. Furberg and J. Solbakk, *Acta Chem. Scand.*, **27**, 2536 (1973).
(13) E. Shefter, M. P. Kotick, and T. J. Bardos, *J. Pharm. Sci.*, **56**, 1293 (1967).
(14) E. Shefter and T. I. Kalman, *Biochem. Biophys. Res. Commun.*, **30**, 878 (1968).
(15) L. F. Power, R. D. G. Jones, J. Pletcher, and M. Sax, *J. Chem. Soc., Perkin Trans. 2*, 1818 (1975).
(16) R. D. G. Jones and L. F. Power, *Acta Crystallogr., Sect. B*, **32**, 1801 (1976).
(17) A. Chiesi Villa, A. Gaetani Manfredotti, M. Nardelli, and M. E. Vidoni Tani, *Acta Crystallogr., Sect. B*, **28**, 356 (1972).
(18) O. Foss, J. Johnsen, and O. Tvedten, *Acta Chem. Scand.*, **12**, 1782 (1958).
(19) I. Bernal and J. S. Ricci, *Acta Crystallogr., Sect. A*, **21**, S104 (1966).
(20) I. L. Karle, J. A. Estlin, and K. Britts, *Acta Crystallogr., Sect. A*, **22**, 273 (1967).
(21) S. W. Peterson and H. A. Levy, *Acta Crystallogr.*, **10**, 70 (1957).
(22) T. Ottersen, LP-76 Computer Program, University of Hawaii, 1976.
(23) "International Tables for X-ray Crystallography", Vol. IV, Kynoch Press, Birmingham, England, 1974, p 55.
(24) T. Ottersen, ABSCO Computer Program, University of Oslo, 1974.
(25) Reference 23, pp 73, 75, and 102.
(26) Reference 23, p 149.
(27) A. J. C. Wilson, *Nature (London)*, **150**, 151 (1942).
(28) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(29) K. Seff, HFIND Computer Program, University of Hawaii, 1971.
(30) C. R. Hubbard, C. O. Quicksall, and R. A. Jacobson, "ALFF, Ames Laboratory Fast Fourier", Iowa State University, 1971.
(31) P. K. Gantzel, R. A. Sparks, and K. N. Trueblood, UCLALS4, American Crystallographic Association Program Library (old) No. 317, modified by T. Ottersen and K. Seff, 1976.
(32) C. K. Johnson, ORTEP-II, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1971.
(33) G. C. Pappalardo and E. Tondello, *Phosphorus Sulfur*, **1**, 5 (1976).
(34) G. C. Pappalardo and S. Gruttadauria, *Gazz. Chim. Ital.*, **105**, 427 (1975).
(35) L. L. Merritt, Jr., and E. D. Schroeder, *Acta Crystallogr.*, **9**, 801 (1956).
(36) K. Nakatsu and H. Yoshioka, *Acta Crystallogr., Sect. A*, **28**, S24 (1972).
(37) A. Kvick and I. Olovsson, *Ark. Kemi*, **30**, 71 (1969).
(38) F. P. Boer, J. W. Turley, and F. P. Van Remoortree, *J. Chem. Soc., Chem. Commun.*, 573 (1972).
(39) A. J. Gordon and R. A. Ford, "The Chemist's Companion", Wiley-Interscience, New York, 1972, pp 145–146.
(40) J. A. Bertrand and J. L. Breece, *Inorg. Chim. Acta*, **8**, 267 (1974).
(41) E. Binamira-Sorlaga, M. Lundeen, and K. Seff, *Acta Crystallogr., Sect. B*, submitted for publication.
(42) L. G. Warner, T. Ottersen, and K. Seff, *Inorg. Chem.*, **13**, 2529 (1974).
(43) I. Bernal, J. L. Atwood, F. Calderazzo, and D. Vitali, *Gazz. Chim. Ital.*, **106**, 971 (1976).
(44) C. Simmons, M. Lundeen, and K. Seff, *Inorg. Chem.*, submitted for publication.

C-5 Substituted Pyrimidine Nucleosides. 2. Synthesis via Olefin Coupling to Organopalladium Intermediates Derived from Uridine and 2′-Deoxyuridine

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Abstract: Organopalladium intermediates derived in situ from C-5 mercurated uridine or 2′-deoxyuridine and Li_2PdCl_4 in methanol react with olefins to produce nucleosides substituted at C-5 by carbon chains. 5-Chloromercuriuridine (**1**) reacts with Li_2PdCl_4 and ethylene in methanol to give 5-(1-methoxyethyl)uridine (**4a**), which can be transformed to 5-ethyluridine (**7a**) by catalytic hydrogenolysis. Seven percent deuterium was incorporated into the side chain when the reaction was run in methanol-d_1, suggesting a mechanism involving a palladium-facilitated hydride shift. 5-Ethyl-2′-deoxyuridine (**7b**) was obtained by the same sequence starting from 5-chloromercuri-2′-deoxyuridine (**2**). The reaction of **2** with Li_2PdCl_4 and propylene in methanol gives three major products, *trans*-5-(1-propenyl)-2′-deoxyuridine (**3b**), 5-(1-methoxypropyl)-2′-deoxyuridine (**4b**), and 5-(1-methoxy-1-methylethyl)-2′-deoxyuridine (**5a**). Styrene and methyl acrylate react with Li_2PdCl_4 and **1** in methanol to give respectively *trans*-5-(2-phenylethenyl)uridine (**3e**) and methyl *trans*-3-(5-uridylyl)propenoate (**3d**). Nucleoside **3d** can also be obtained by the reaction between 5-iodouridine, methyl acrylate, and a catalytic amount of palladium acetate. 5-(4-Hydroxypentyl)uridine (**7d**) and 5-pentyluridine (**7e**) were obtained from **1** and 4-penten-2-ol after palladium-catalyzed coupling and catalytic hydrogenation. 1-Benzyloxy-4-penten-2-ol was employed in a synthesis of 5-(4,5-dihydroxypentyl)-2′-deoxyuridine (**7f**) following a similar procedure.

Introduction

Pyrimidine nucleosides substituted at the C-5 position constitute a class of biologically significant molecules. Within this class one may distinguish three categories. C-5 substituted pyrimidine nucleosides are found as constituents of transfer RNA[1-4] and DNA.[1,5-8] Derivatives of 2′-deoxyuridine with C-5 substituents no larger than the *n*-butyl group are of interest as chemotherapeutic agents.[9-12] Other derivatives have found application in the biochemical and physicochemical study of biological macromolecules.[13-17] In the search for new nucleoside analogues, antiviral agents, and more sophisticated biological probes, we have sought a new synthetic route to C-5 substituted pyrimidine nucleosides which would allow us to easily attach a wide array of functional groups via carbon chains at C-5. Previous efforts to obtain 5-alkyl-2′-deoxyuridines as antiviral agents illustrate the problems to be expected in any synthesis of a C-5 substituted pyrimidine nucleoside via a route requiring glycosidic bond formation at some stage during the synthesis.[10,18-23]

We recently reported that pyrimidine nucleosides substituted at C-5 by carbon chains may be readily obtained by the reaction of C-5 mercurated derivatives of uridine and 2′-deoxyuridine[13,24] with Li_2PdCl_4 and olefins.[25] The present paper reports an elaboration of those preliminary results.

Results and Discussion

The reaction of C-5 mercurated nucleosides with Li_2PdCl_4 and monosubstituted olefins in methanol is complicated by a problem which was apparently not encountered in the original studies of Heck.[26] In addition to the expected nucleoside substituted olefins, in some instances substantial amounts of C-5 α-methoxyalkyl nucleoside are formed. The major product from reaction of 5-chloromercuriuridine (**1**) with 0.1 M Li_2PdCl_4 and ethylene in methanol was not the expected 5-

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Table I. Carbon-13 Chemical Shifts in C-5 Substituted Pyrimidine Nucleosides.[a]

nucleoside	carbon positions[b]														
	C-2	C-4	C-5	C-6	C-1′	C-2′	C-3′	C-4′	C-5′	C-1″	C-2″	C-3″	C-4″	C-5″	
4a	155.03	168.82	117.44	140.16	91.93	71.45	76.22	86.22	62.57	74.96	21.65				OCH_3 58.04
7b	153.72	168.20	119.29	138.99	87.49	41.02	72.67	88.81	63.30	21.85	14.19				
7c	153.82	168.46	117.48	139.68	91.49	71.54	76.08	86.32	62.72	30.33	23.21	15.02			
8a	153.77	unobservable	117.44	137.97	91.73	71.50	76.28	86.27	62.43	27.65	22.97				α-CH_3 22.97
7d	153.82	168.16	117.34	139.72	91.44	71.50	76.03	86.32	62.67	39.50	26.04	28.24	69.84	24.14	
7e	153.82	168.00	117.78	139.53	91.44	71.54	76.13	86.32	62.67	32.72	28.19	29.36	24.04	15.61	
7f	153.72	168.20	117.24	140.01	87.54	40.97	72.67	88.90	63.30	33.80	25.99	28.14	73.79	67.69	

[a] Spectra were run in D_2O; shifts given in parts per million relative to external Me_4Si; spectra are completely decoupled. [b] C-2, C-4, C-5, and C-6 refer to carbon atoms of the pyrimidine ring, C-1′, C-2′, C-3′, C-4′, and C-5′ refer to carbon atoms of the sugar, and C-1″, C-2″, C-3″, C-4″, C-5″ refer to carbon atoms of the C-5 side chain.

vinyluridine (**3a**) but instead 5-(1-methoxyethyl)uridine (**4a**). The structure of **4a** was established beyond question by ^1H NMR, ^{13}C NMR (Table I), UV, and mass spectrometry (see Experimental Section) and by its transformation to 5-ethyluridine[27] (**7a**) with H_2 and Pd/C.

A second minor product, determined in one run to be 6% of the total nucleosides after silica gel chromatography, was observed during most preparations of 5-(1-methoxyethyl)-uridine (**4a**). The ^1H NMR spectrum of this product corresponded exactly to that published for 5-vinyluridine (**3a**).[21] However, we were unable to successfully purify this product for further characterization owing to its facile decomposition to a white, polymeric substance.[28] Despite numerous modifications of the reaction conditions 5-vinyluridine could only be obtained in low yield and then not successfully purified. Acetonitrile, which has worked with particular success for the coupling reaction using simple aryl mercurials,[26] failed in reactions of the highly insoluble mercurinucleosides. The reaction rates were extremely slow (little reaction after 2 days) giving only minute amounts of nucleoside products.

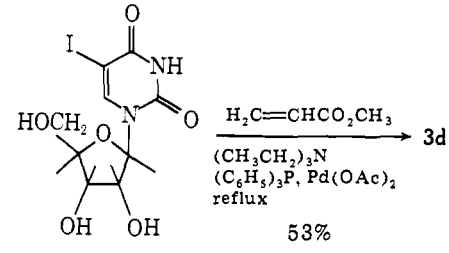
In many instances we have required a pyrimidine nucleoside with a C-5 side chain saturated at carbons 1 and 2. Mixtures of the 1-methoxyalkyl and alkenyl C-5 substituted pyrimidine nucleosides as obtained from the coupling reaction could be subjected to hydrogen in the presence of 10% Pd/C with reduction of the exocyclic double bond and concomitant hydrogenolysis at the methyl ether linkage. In order to accomplish this step mercuric ion was removed from the crude reaction mixture by borohydride reduction to mercury metal. The crude mixture from reaction between 5-chloromercuriuridine (**1**), Li_2PdCl_4, and ethylene, treated in this way and subjected to hydrogenation, gave crude 5-ethyluridine (**7a**) in yields as high as 86% after silica gel chromatography.[29]

5-Ethyl-2′-deoxyuridine (**7b**) was prepared from 5-chloromercuri-2′-deoxyuridine (**2**) in 57% yield following the same procedure.

When **1** was treated with 0.2 equiv of Li_2PdCl_4, 1 equiv of cupric chloride, and ethylene in methanol, followed by catalytic hydrogenation over Pd/C, 5-ethyluridine was obtained in 48% yield after chromatography and recrystallization.

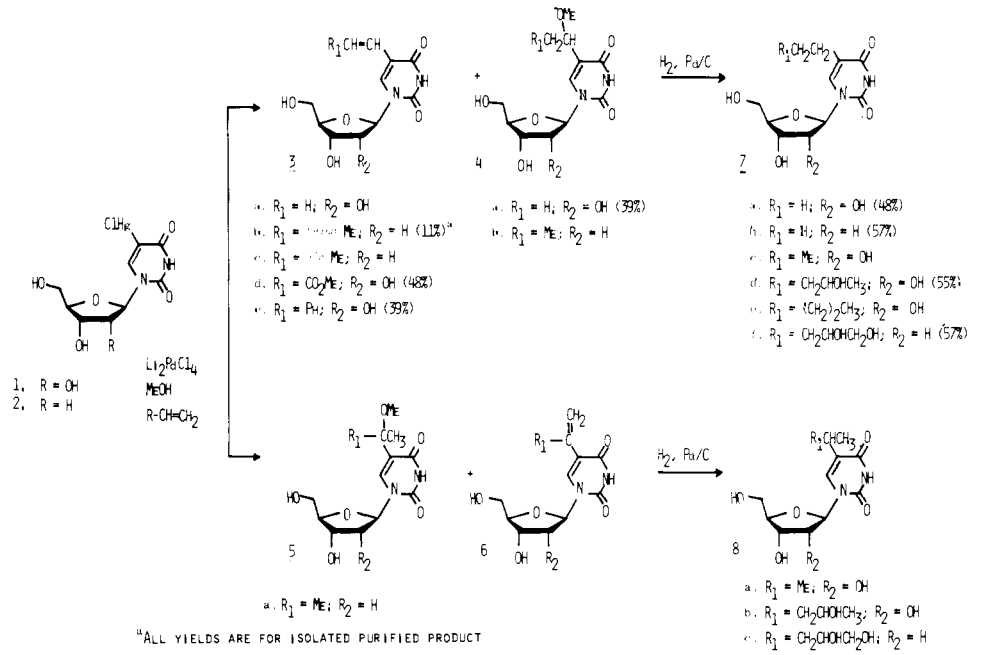
The organopalladium coupling reaction occurs as readily with numerous monosubstituted (terminal) olefins. Three classes of olefins were examined; conjugated, nonconjugated, and allylic halides.[30] Conjugated olefins exhibit the least complex behavior. In the examples described here as well as examples to be reported elsewhere the carbon–carbon bond is formed between C-5 and the terminal carbon of the olefin. In contrast nonconjugated olefins show coupling at both C-1 and C-2 of the olefin. Furthermore, the conjugated olefins give only olefinic products. α-Methoxy adducts from reactions in methanol have never been observed. When **1**, Li_2PdCl_4, and styrene were combined in methanol a single major product, *trans*-5-(2-phenylethenyl)uridine (**3e**), was isolated and purified in 39% yield. The trans stereochemistry was postulated on the basis of the ^1H NMR spectrum since the doublets at δ 6.89 and 7.48 had a coupling constant of 17 Hz.

Under similar conditions **1**, Li_2PdCl_4, and methyl acrylate gave methyl *trans*-3-(5-uridylyl)propenoate (**3d**) as the major product. Nucleoside **3d** could be obtained also by an alternate procedure[31] starting with 5-iodouridine and utilizing only a catalytic amount of palladium. When 5-iodouridine was refluxed for 16 h in methyl acrylate with triethylamine, triphenylphosphine, and only 5 mol % palladium acetate, nucleoside **3d** was obtained in 53% yield.



The reaction with nonconjugated olefins in methanol is far more complex. For any olefin $RCH{=}CH_2$ one may expect to obtain variable amounts of at least four nucleosides **3–6.** Since in many instances our goal has been the attachment of various functional groups via nonfunctional spacers at C-5, separation of nucleosides **3–6** is unnecessary. The carbon–carbon double bonds of **3** and **6** and the α-methoxy function of **4** and **5** undergo catalytic hydrogenation and hydrogenolysis, respectively, under the same conditions, H_2 over Pd/C. The problem then becomes one of separating the saturated side chain isomers **7** and **8**, a problem which may be either relatively easy or difficult depending on the identity of R. A mixture of 5-propyluridine (**7c**) and 5-isopropyluridine (**8a**) was obtained as a crystalline solid (60% yield) from the two-step sequence involving the reaction of **1**, Li_2PdCl_4, and propylene in methanol followed by reduction by H_2 over 10% Pd/C. By ^1H NMR spectroscopy the relative amount of **7c** to **8a** was estimated to be four to one. The two isomers could not be completely separated by thin layer chromatography on silica gel or by column chromatography on Bio-Gel P-2 or silica gel. Since pure 5-propyluridine could be obtained in substantial amounts by catalytic hydrogenation of 5-allyluridine[30] and its structure substantiated on the basis of spectroscopic and analytical data we are confident in assigning structures **7c** and **8a** to the mixture obtained in the propylene reaction on the basis of ^1H NMR, UV, and elemental analysis. The ^{13}C NMR spectrum of the mixture of nucleosides **7c** and **8a** (Table I) was compared to a spectrum of pure **7c** in order to establish chemical shifts for the carbons of **8a.** Sugar and heterocyclic carbon-13 shifts were established by comparison of our spectra with the published data of Jones et al.[32] and Breitmaier et al.,[33] and the chemical shifts of the

Scheme I



side chain carbon atoms assigned by comparison and analysis according to Levy and Nelson.[34]

The occurrence of nucleosides **3–6** from the reactions of nonconjugated olefins has been shown most definitively in the reaction of propylene with the organopalladium derivative derived from 5-mercuri-2′-deoxyuridine.[35] Finding isomeric olefins was not unexpected since it has been previously shown that phenylmercuric acetate, palladium acetate, and propylene in methanol give the four isomers, *trans*-1-phenyl-1-propene (60%), *cis*-1-phenyl-1-propene (9%), 1-phenyl-2-propene (15%), and 2-phenyl-2-propene (16%).[36] However, in addition we find isomeric methoxyalkyl derivatives. Chromatography of the crude reaction mixture on silica gel and Bio-Gel P-2 led to separation of nucleosides **3b, 4b,** and **5a.** Nucleosides **3c** and **6** occurred in relatively minor amounts and could not be separated from each other.

From the integration of the ^{1}H NMR spectrum of the reaction mixture prior to chromatography the relative amounts of nucleosides **3b, 4b,** and **5a** were estimated to be 2.3:1.4:1.0. After chromatography and recrystallization from water the yield of purified **3b** was 11%. Structures of **3b, 3c, 4b, 5a,** and **6** were assigned principally on the basis of ^{1}H NMR spectra.

For example, the ^{1}H NMR spectrum of **3b** showed, in addition to the proton signals which could be attributed to the deoxyribose, a singlet at δ 7.86 (1 H), a doublet (J = 5 Hz) at δ 1.80 (3 H), and a complex centered at δ 6.18 (2 H) overlapping the triplet due to the anomeric C-1′ proton of the sugar moiety. As much as the δ 6.18 pattern can be discerned, it is similar to the signals observed for the olefinic protons of *trans*-propenylbenzene[37] but vastly different from the signals obtained for either *cis*-propenylbenzene[37] or α-methylstyrene.[38] Elemental analysis, UV, and mass spectrometry, as well as a direct comparison to **3b** prepared by the rhodium-catalyzed isomerization of 5-allyl-2′-deoxyuridine,[30] provided further proof for the structure.

5-(1-Methoxypropyl)-2′-deoxyuridine (**4b**) and 5-(1-methoxy-1-methylethyl)-2′-deoxyuridine (**5a**) showed characteristic UV maxima at 266 nm and unambiguous ^{1}H NMR spectra. Nucleosides **4b** and **5a** could neither be crystallized nor obtained free of water by drying in vacuo. They undergo thermal decomposition in the mass spectrometer displaying complex volatilization profiles and exceedingly complex spectra. The base ion in the spectrum of **5a** was the fragment at *m/e* 152 corresponding to 5-(1-methylethenyl)uracil. The structures of **3c** and **6** were assigned solely on the basis of a ^{1}H NMR spectrum of the mixture. The resonance patterns observed for the olefinic and methyl protons were virtually identical with those reported for *cis*-propenylbenzene and α-methylstyrene.

One of our primary goals was the synthesis of 5-(4,5-dihydroxypentyl)-2′-deoxyuridine (**7f**). As a model for the reaction we first attempted the coupling reaction between the more readily available olefin 4-penten-2-ol and nucleoside **1**. When 4-penten-2-ol and nucleoside **1** were allowed to react with Li_2PdCl_4 in methanol and the mixture was subjected to catalytic hydrogenation two products in relative yields of 17 and 83% were obtained. The major product was clearly nucleoside **7d** on the basis of ^{1}H NMR, mass spectrum, and analytical data (see Experimental Section). However, the minor product was not, as first assumed, the result of coupling at C-2 of the olefin to give (after catalytic hydrogenation) an isomer of **7d.** On thin layer chromatography it migrated considerably faster than **7d,** and on the basis of ^{1}H NMR, ^{13}C NMR, and mass spectrum the compound was established to be 5-pentyluridine (**7e**). The mass spectrum shows a molecular ion peak at *m/e* 314 and major fragments at *m/e* 183 (B + H), 184 (B + 2H), 225 (BCH_2CHOH), 211 (M − CH_2O), and 133 (ribose). The molecular formula, $C_{14}H_{22}N_2O_6$, was established by determining the exact mass of the molecular ion at *m/e* 314. Unequivocal assignment of the C-5 chain as the *n*-pentyl group was made on the basis of the proton decoupled ^{13}C NMR spectrum (Table I).

In order to synthesize **7f** a coupling reaction between **2** and 1-benzyloxy-4-penten-2-ol was carried out. The olefin was prepared[39] by the Grignard reaction between allylmagnesium bromide and α-benzyloxyacetaldehyde,[40] which in turn was readily available from the periodate oxidation of 1-*O*-benzylglycerol. The reaction between 5-mercuri-2′-deoxyuridine,[35] Li_2PdCl_4, and excess 1-benzyloxy-4-penten-2-ol followed by catalytic hydrogenation over Pd/C gave the desired 5-(4,5-dihydropentyl)-2′-deoxyuridine (**7f**) in 57% yield after silica gel chromatography. Although by TLC the material appeared to be a single compound, the appearance of a doublet (J = 7 Hz) at δ 1.06 suggested that a small amount of 5-(1-methyl-3,4-dihydroxybutyl)-2′-deoxyuridine (**8c**) was present. Recrystallization of the mixture from acetone gave analytically pure **7f** with no trace of **8c** by ^{1}H NMR.

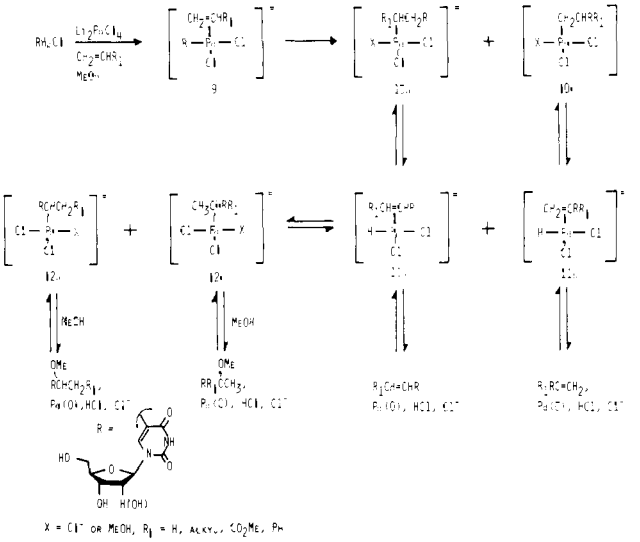
Apart from examining the scope of the coupling reaction with various olefins we have explored further modifications such as utilizing other group 8 metals in place of palladium and acetylenes in place of olefins. For the most part these have met with little success. For example, rhodium, which Heck found could replace palladium in the coupling reaction,[26] was found to convert mercurinucleosides to the parent nucleoside.[30] Along similar lines when the complex $Rh(CH_3)I_2(PPh_3)_2$[41] was allowed to react with mercurinucleoside **1** in HMPA at 70 °C, the only isolable product was 2′-deoxyuridine. 2′-Deoxythymidine could not be detected. Heck also found that terminal acetylenes could be converted to aryl-substituted acetylene derivatives by the coupling reaction utilizing either arylmercurials[42] or aryl iodides[43] to create the organopalladium intermediate in situ. We attempted to couple phenylacetylene and 4-pentyn-1-ol to 5-chloromercuriuridine (**2**) following Heck's procedure and obtained uridine as the only identifiable product. When 5-iodouridine with either of these acetylenes, palladium acetate, triethylamine, and triphenylphosphine was found to give a complex mixture of products, further exploration along these lines was discontinued.

Mechanism

The mechanism of formation of nucleosides **3** and **6** probably resembles that proposed for arylation of olefins with organopalladium compounds by Heck.[44] The initial transformation (Scheme II) of **1** to complex **9** requires π-complex formation between the olefin and Pd(II) followed by metal–metal exchange through chloride bridged ions[45] with liberation of $HgCl_2$ and creation of a σ bond between C-5 of the pyrimidine and palladium. Insertion of the olefin into the Pd–C σ bond would then give complexes **10a** and **10b.** Cis elimination of Pd–H leads to π complexes **11a** and **11b** from **10a** and **10b,** respectively. Dissociation of the π complexes would give Pd(0), hydrogen chloride, and nucleosides **3** and **6**. A postulated pathway for the introduction of the α-methoxy group into the side chain is shown in Scheme II. A number of experiments give results compatible with this mechanism but incompatible with other possible mechanisms.

When the coupling reaction between **1**, ethylene, and Li_2PdCl_4 was carried out in the presence of triethylamine or magnesium oxide to scavenge HCl produced in the reaction, the relative yields of 5-vinyluridine (**3a**) and 5-(1-methoxyethyl)uridine (**4a**) were not appreciably changed. The same reaction in methanol-d_1 gave **4a** with only 6–7% deuterium incorporation into the side chain methyl group as measured by mass spectrometry. These results were reproducible and independent of whether $NaBH_4$ or $NaBD_4$ was used in the workup. In order for the deuterium incorporation studies to be meaningful **4a** was purified prior to mass spectral analysis only by elution with water on Bio-Gel P-2. Silica gel chromatography eluting with methanol-chloroform would have decreased the apparent deuterium incorporation since 5-vinyluridine appears to be transformed partially to **4a** and polymer during chromatography. It is unlikely that **4a** is formed via methoxymercuration of the vinyl group followed by demercuration with H_2S or $NaBH_4$. Thin layer chromatography shows little difference in product composition before and after $NaBH_4$ or H_2S treatment. Furthermore the nucleosides can be separated from the reaction mixture and mercuric ion by chromatography on Bio-Gel P-2 (water elution). Finally, nucleoside **3b** when stirred with Li_2PdCl_4, propylene, $HgCl_2$, and HCl in methanol was not converted to **4b** nor in any other way transformed. Methoxymercuration of the carbon–carbon double bond by $HgCl_2$ was expected to be an unlikely occurrence; however, lack of reactivity toward methanolic HCl was unexpected. These experiments clearly indicate that nucleoside **3** is not the obligatory precursor to **4** either through acid- (HCl) catalyzed addition of MeOH or by way of methoxymercuration with subsequent reductive cleavage of the carbon–mercury bond (by $NaBH_4$ or H_2S). The mechanism, in order to explain the low level of deuterium incorporated at the terminal methyl group of **4a,** must involve transfer of hydride from some other location in the molecule. Migration of Pd along a carbon chain via sequential interconversions of a Pd–C σ bonded species and the corresponding hydridochloropalladium π-alkene complexes until the most thermodynamically stable species is arrived at has been indicated in several instances.[46-48]

Scheme II. Mechanism of Formation of Nucleosides 3–6 via an Organopalladium Intermediate



The transformation of **10a** to **12a** via the intermediate hydridochloropalladium π-alkene complex **11a** therefore seems plausible. The pathway by which methanol replaces palladium in the transformation **12a** to **4** remains a matter for speculation. It is possible that **12a** (X = MeOH) could collapse directly to **4** in an intramolecular process, or alternately **12a** could give the carbocation $RC^+HCH_2R_1$ and Pd(0), HCl. Nucleoside **4** would then result from the reaction of this carbocation with methanol. The high degree of stability predicted for this cation in polar solvents seems to lend favor to the latter proposal.

The mechanism by which 5-pentyluridine (**7e**) was formed in the two-step sequence involving coupling 1-penten-4-ol to **1** followed by catalytic hydrogenation is unknown. 5-Pentyluridine appeared only after catalytic hydrogenation. Owing to the complexity of the reaction mixture prior to catalytic hydrogenation we have not attempted to isolate and purify precursors to **7e.**

Conclusion

The organopalladium coupling reaction is a synthetically useful method for preparing uridine and 2′-deoxyuridine analogues substituted by carbon chains at C-5. 5-Ethyl-2′-deoxyuridine and 5-ethyluridine are readily prepared in high yield by the two-step sequence involving coupling of the ethylene to the mercurinucleoside followed by catalytic hydrogenolysis of the intermediate methoxyethyl nucleosides. With longer chain nonconjugated terminal olefins coupling at C-1 predominates but products from C-2 coupling have also been found as exemplified by the reaction with propylene. In most cases the resulting isomeric nucleosides obtained after catalytic hydrogenolysis can be separated by chromatography and recrystallization. Conjugated olefins apparently show coupling only at the terminal carbon of the double bond.

5-Chloromercuricytidine and 5-chloromercuri-2′-deoxycytidine[24] undergo analogous coupling reactions via organopalladium intermediates and this will be the subject of a separate report.

Experimental Section

Proton magnetic resonance spectra (^{1}H NMR) were taken on either a Varian EM360 60-MHz instrument or a Fourier transform NMR, JEOL Model PS100. Sodium 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propionate was employed as the internal reference for spectra run in D_2O. ^{13}C NMR were also obtained on the latter instrument. Ultraviolet spectra were measured on a Cary 17 spectrometer in water with pH extremes obtained by addition of 1.0 M NaOH or HCl. Infrared spectra were obtained on a Beckman IR-8 in solid KBr. Low-resolution mass spectra were obtained on a Model 3200 Finnigan mass spectrometer at 70 eV and high-resolution spectra were obtained on a Du Pont 492h instrument. Column chromatography was done on Woelm, activity 1, type 204 silica gel and on Bio-Gel P-2. Analytical thin layer chromatography was carried out on E. Merck precoated silica gel F-254 (0.25 mm) plastic backed TLC sheets cut to 35 × 110 mm. The sheets were developed in the specified solvent systems in 12-cm high wide mouth jars lined with filter paper. The plates were removed from the jars immediately after the solvent front had traveled 10 cm. Solvent systems were I, MeOH-$CHCl_3$ (1:3 v/v), and II, MeOH-CH_3CO_2Et (15:85 v/v). For reference 2′-deoxyuridine was found to have R_f 0.37 in system I and R_f 0.29 in system II. All solvents and reagents were reagent grade. Uridine and 2′-deoxyuridine were purchased from Sigma Chemical Co. Water was deionized and then distilled through glass. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., and by the microanalytical laboratory at the University of California, Berkeley. Melting points were taken on a Büchi 510 melting point apparatus, and are uncorrected.

Coupling reactions between ethylene or propylene and mercurinucleosides were carried out at 20–30 psi in Parr bottles utilizing an apparatus similar to that described by Barefield.[49] The apparatus was slightly modified from the one described by the addition of a separate permanent connection to a hydrogen cylinder, in addition to a connection adapted for easy exchange of lecture bottles.

5-(1-Methoxyethyl)uridine (4a). 5-Chloromercuriuridine (**2**,[24] 1.2473 g, 2.60 mmol) was suspended in a solution of Na_2PdCl_4 in methanol (0.1 M, 26.8 mL) in a 500-mL Parr bottle and the mixture stirred under an ethylene atmosphere (21 → 19.5 psig) for 9 h. A palladium metal mirror was observed to occur on the walls of the apparatus during the course of the reaction. The solution was gravity filtered and the black precipitate washed with three 10-mL portions of methanol. H_2S was bubbled into the combined filtrates for 30 s, and the solution immediately gravity filtered. The black sulfide precipitate was washed with methanol (30 mL) and the combined methanol solutions evaporated to give a nearly colorless residue. The residue was dissolved in methanol (3 mL) and applied to a silica gel column (50 g, 2.2 cm diameter). Elution with 20% methanol-chloroform gave the product in fractions 9–17 (11-mL fractions) along with minor amounts of other components as observed by TLC. The residue from evaporation of combined fractions 9–17 was rechromatographed on a silica gel column (60 g, 2.2 cm diameter) eluting with 15% methanol-chloroform. Fractions 42–58 (5-mL fractions) showed a single spot on TLC. These were combined, the solvent removed in vacuo, and the resulting colorless oil dissolved in water (4 mL), filtered, and lyophilized. Yield of pure white solid **4a** was 304.5 mg (1.01 mmol, 39%): softening begins at 54 °C but no clear melting point could be observed; ^{1}H NMR (D_2O) δ 8.02 (1 H, s, HC-6), 6.03 (1 H, d, J = 3 Hz, HC-1′), 4.37 (4 H, m, HC-2′, HC-3′, HC-4′), 3.98 (2 H, broad s, H_2C-5′), 3.39 (3 H, s, $-OCH_3$), 1.43 (3 H, d, J = 6.5 Hz, C-CH_3); mass spectrum m/e (rel intensity) 302 (2, molecular ion), 287 (5, M − CH_3), 272 (15), 211 (2, $BHCH_2COH$), 171 (3, B + 2H), 170 (5, B + H), 155 (100, BH − CH_3), 132 (12, ribosyl). Anal. ($C_{12}H_{18}N_2O_7$) C, H, N. TLC, system I, R_f 0.37; system II, R_f 0.30.

The ratio of 5-vinyluridine (**3a**) to **4a** was determined by integration of the ^{1}H NMR spectrum prior to silica gel chromatography. 5-Vinyluridine: ^{1}H NMR (D_2O) δ 8.02 (1 H, s, HC-6), 6.50 (1 H, dd, J = 11 and 17.5 Hz), 5.96 (1 H, m, HC-1′), 5.81 (1 H, dd, J = 17.5 and 2 Hz), 5.31 (1 H, dd, J = 11 and 2 Hz), 4.3 (3 H, m), 3.77 (2 H, m, H_2C-5′).

The preparation of **4a** in CH_3OD was carried out by a similar procedure; however, Li_2PdCl_4 was used in place of Na_2PdCl_4. Chromatography as described above gave pure product by TLC analysis. The ratio of the intensity of the M + 2 ion at m/e 304 to the ion at m/e 303 was 1:5.6 in one experiment and 1:5.3 in a second experiment. A molecular ion peak at m/e 302 was observed only when the concentration of sample was too low to give a reproducible M + 1 ion. At high sample loads ions at m/e 303 and 304 were reproducibly observed. When compared to the ratio of these peaks for **4a** prepared in CH_3OH (1:8.4) the amount of deuterium incorporated could be estimated as 6%.

5-Ethyluridine (7a). Method A. 5-Chloromercuriuridine (0.656 g, 1.369 mmol) and 0.1 M Li_2PdCl_4 (13.7 mL) were stirred under ethylene at atmospheric pressure for 3 h. The reaction mixture was filtered washing the precipitate with methanol (10 mL). The filtrate was cooled in an ice bath and solid $NaBH_4$ (100 mg) added in small portions over a period of 4 min. The solution was filtered and washed with methanol until the total filtrate volume was 50 mL. Pd/C (10%, 100 mg) was added and the mixture stirred under H_2 (15 psig) for 16 h. The mixture was filtered and the solvent evaporated from the filtrate in vacuo to leave a colorless oil and a white solid. The oil was dissolved in a minimum amount of methanol-acetone (2:98) and centrifuged to remove the insoluble salts. The methanol-acetone soluble residue was applied directly to a silica gel column (50 g, 2.2 cm diameter) and eluted with methanol-acetone (2:98). The fractions (6 mL, 11–26) showing a UV-absorbing component on TLC at R_f 0.47 (acetone eluent) were combined and evaporated and the residue rechromatographed on silica gel (50 g) eluting with ethyl acetate-ethanol (3:1). Fractions 14–28 were combined and the solvent was evaporated to give 323.7 mg of 5-ethyluridine (86% yield). This crude product contains no other nucleosides but is slightly contaminated with inorganic salts. Recrystallization from acetone with low recovery gave analytically pure product melting at 186–187 °C (lit.[27] mp 184–186 °C).

Method B. A 250-mL Parr bottle was charged with 5-chloromercuriuridine (0.603 g, 1.26 mmol), $CuCl_2$ (0.349 g, 2.52 mmol), 0.1 M Li_2PdCl_4 (2.5 mL), and methanol (10 mL). The mixture was stirred under ethylene (19 → 15 psig) for 12 h. The mixture was filtered to give a lime-green filtrate, which was concentrated and passed through a short column of Chelex 100 (Na^+ form, 20 g) eluting with methanol. Cu(II) ions were retained on the column but Cu(I) ions passed through with the nucleosides. The fractions showing a spot on TLC at R_f 0.66 (acetone eluent) were combined and treated with H_2S until precipitation of the black sulfides was complete. Filtration gave a clear, colorless filtrate which was evaporated in vacuo to an oil. The oil was redissolved in methanol (30 mL) and the methanol again removed in vacuo. The residue was dissolved in methanol (30 mL) and combined with 10% Pd/C (100 Mg) in a 500-mL Parr bottle. After stirring under H_2 (19 psig) for 18 h, the mixture was filtered and the filtrate evaporated in vacuo. The residue was chromatographed on silica gel (50 g, 1.8 cm diameter) eluting with a stepwise gradient of methanol-chloroform (from 5% to 20% methanol in 5% steps). Fractions showing a single spot at R_f 0.47 on TLC (acetone eluent) were combined and evaporated in vacuo to give 164 mg of white star crystals (48% yield) of analytically pure 5-ethyluridine: mp 185–187 °C; IR (KBr) 1648, 1706 cm^{-1}; ^{1}H NMR (D_2O) δ 1.07 (3 H, t, J = 7.5 Hz, CH_3), 2.30 (2 H, q, J = 7.5 Hz, $-CH_2-$), 3.89 (2 H, br s, H_2C-5′), 4.22 (3 H, m, HC-2′, HC-3′, HC-4′), 5.92 (1 H, d, J = 3.5 Hz, HC-1′), 7.72 (1 H, s, HC-6); UV (H_2O) λ_{max} 266 nm. Anal. ($C_{11}H_{16}N_2O_6$) C, H, N. TLC, system I, R_f 0.34; system II, R_f 0.32.

5-Ethyl-2′-deoxyuridine (7b). A 250-mL Parr bottle was charged with 5-chloromercuri-2′-deoxyuridine (0.424 g, 0.915 mmol) and 0.1 M Li_2PdCl_4 in methanol (9.15 mL). The solution was stirred under ethylene (17 psig) for 12 h at room temperature, and then filtered to remove Pd(0). The filtrate was cooled to 0 °C and treated with $NaBH_4$ (53 mg) until reduction of mercuric ion to mercury was complete. The reaction mixture was filtered and the filtrate evaporated in vacuo to give a colorless oil, which was then redissolved in methanol (50 mL) and stripped in vacuo twice. The residue was dissolved in a mixture of methanol (25 mL) and water (4 mL) and subjected to catalytic hydrogenation over 10% Pd/C (98 mg) for 24 h (24 psig H_2). The reaction mixture was filtered, the catalyst washed thoroughly with methanol, and the combined filtrates evaporated in vacuo. Chromatography on silica gel (60 g) gave 118.8 mg of 5-ethyl-2′-deoxyuridine (57%) melting at 146–150 °C. Analytically pure nucleoside was obtained as clear, long needles on recrystallization from acetone: mp 153–153.5 °C (lit.[10] mp 152–153 °C); IR (KBr) 1658, 1706 cm^{-1}; ^{1}H NMR (D_2O) δ 1.11 (3 H, t, J = 7.5 Hz, CCH_3), 2.37 (4 H, overlapping q's and dd, $-CH_2CH_3$ and H_2C-2′), 3.84 (2 H, narrow m, H_2C-5′), 4.05 (1 H, m, HC-3′), 4.50 (1 H, m HC-4′), 6.33 (1 H, t, J = 6.5 Hz, HC-1′), 7.69 (1 H, s, HC-6); UV (H_2O) λ_{max} 266 nm. Anal. ($C_{11}H_{16}N_2O_5$) C, H, N. TLC, system I, R_f 0.47; system II, R_f 0.43.

5-Propyluridine (7c) and 5-Isopropyluridine (8a). A Parr bottle was charged with nucleoside **1** (0.575 g, 1.20 mmol), 0.1 M Li_2PdCl_4 (12.0 mL) in methanol, and methanol (5 mL), and stirred under propylene (23 psig) for 22 h. The workup included filtration, H_2S treatment of the filtrate for 30 s, filtration, and evaporation of methanol from the filtrate to give a colorless oil. The crude product was chromatographed on silica gel (50 g) eluting with 16% methanol-chloroform (v/v) and the total nucleosides that eluted were subjected to catalytic hydrogenation (20 psig, 24 h) in methanol (30 mL) with 10% Pd/C (100 mg) as catalyst. The reaction mixture was then filtered and the methanol removed in vacuo to give 205.3 mg of white crystals (60% yield). Recrystallization from ethanol gave crystals slightly enriched in **7c**. Analytical data were obtained on recrystallized product composed of 20% **8a** and 80% **7c**, mp 191–193 °C; 5-propyluridine ^{1}H NMR (D_2O) δ 0.90 (3 H, t, J = 7 Hz, CH_3), 1.48 (2 H, sextet, J = 7 Hz, $-CH_2CH_2CH_3$), 2.27 (2 H, t, J = 7 Hz, $-CH_2CH_2CH_3$), 3.93 (2 H, broad s, H_2C-5′), 4.25 (3 H, m, HC-2′, HC-3′, HC-4′), 5.95 (1 H, d, J = 3 Hz, HC-1′), 7.80 (1 H, s, HC-6); 5-isopropyluridine ^{1}H NMR, in addition to the signals at δ 3.93, 4.25, 5.95, and 7.80, peaks are observed at δ 1.13 (6 H, d, J = 7 Hz, CH_3) and 2.82 (1 H, heptet, J = 7 Hz, $-CH(CH_3)_2$); mass spectrum[50] *m/e* (rel intensity) 286 (9, molecular ion), 197 (3, BCH_2CHOH), 154 (100, B + H), 155 (51, B + 2H), 133 (17, ribosyl), 183 (6, B + CHOH). Anal. ($C_{12}H_{18}N_2O_6$) C, H, N. TLC, system I, R_f 0.38; system II, R_f 0.37.

Reaction of 5-Mercuri-2′-deoxyuridine with Li_2PdCl_4 and Propylene in Methanol. A 500-mL Parr bottle was charged with 5-mercuri-2′-deoxyuridine (1.008 g, 2.36 mol) and 23.6 mL of 0.1 M Li_2PdCl_4 in methanol. The mixture was stirred under propylene (24 → 22 psig) for 2 h. The solution was filtered and the filtrate treated with H_2S gas until precipitation of brown HgS was complete (~30 s). The solution was filtered and the solvent removed in vacuo. Chromatography of the residue on silica gel (150 g, 60 × 2.5 cm column) eluting with a methanol-chloroform gradient (10–23% methanol v/v) gave partial separation of the three major components. Fractions (7 mL) were collected. Early fractions (56–61) were enriched in 5-(1-methoxypropyl)-2′-deoxyuridine (**4b**), middle fractions (62–69) were enriched in *trans*-5-(1-propenyl)-2′-deoxyuridine (**3b**), and late fractions (70–76) were enriched in 5-(1-methoxy-1-methylethyl)-2′-deoxyuridine (**5**). Each of these fraction groups was applied separately to a Bio-Gel P-2 column (2 × 64 cm) eluting with water. Nucleosides **4b** and **5** are eluted first, followed by **3c** and **6**, and then **3b**. Lyophilization of fractions corresponding to peak **3b** gave a white solid which was recrystallized from water to give analytically pure **3b** (11% yield, combined from three Bio-Gel P-2 columns): mp 172–174 °C; ^{1}H NMR (D_2O)[51] δ 1.81 (3 H, d, J = 5 Hz, CH_3), 2.39 (2 H, dd, J = 6 Hz, H_2C-2′), 3.82 (2 H, m, H_2C-5′), 4.02 (1 H, m, HC-3′), 4.49 (1 H, m, HC-4′), 5.98 and 6.18 (2 H′, m, $-HC{=}CH-$), 6.21 (1 H, t, J = 6 Hz, HC-1′), 7.82 (1 H, s, HC-6); mass spectrum *m/e* (rel intensity) 268 (3, molecular ion) 179 (5, BCH_2CHOH), 153 (40, B + 2H), 152 (100, B + H), 137, (34, BH − CH_3), 117 (60, deoxyribosyl). Anal. ($C_{12}H_{16}N_2O_5$) C, H, N. TLC, system I, R_f 0.49; system II, R_f 0.48.

Lyophilization of fractions corresponding to the peaks corresponding to **4b** and **5** gave a mixture of these nucleosides as a colorless oil. **4b** and **5** could be separated to no greater than 95% purity by further chromatography on silica gel (as described above). ^{1}H NMR **4b** (D_2O) δ 0.90 (3 H, t, J = 7 Hz, $-CHCH_2CH_3$), 1.73 (2 H, m, $-CHCH_2CH_3$), 2.44 (2 H, dd, J = 6 Hz), 3.33 (3 H, s, $-OCH_3$), 3.86 (2 H, m, H_2C-5′), 4.12 (1 H, m, HC-3′), 4.32 (1 H, m, $-CHCH_2CH_3$), 4.53 (1 H, m, HC-4′), 6.33 (1 H, t, J = 6 Hz, HC-1′), 7.83 (1 H, s, HC-6); ^{1}H NMR **5** (D_2O) δ 1.53 (6 H, s, $-C(CH_3)_2$), 2.40 (2 H, dd, J = 6 Hz, H_2C-2′), 3.82 (2 H, m, H_2C-5′), 4.08 (1 H, m, HC-3′), 4.48 (1 H, m, HC-4′), 6.33 (1 H, t, J = 6 Hz, HC-1′), 7.83 (1 H, s, HC-6).

Nucleosides **4b** and **5** were subjected to elemental analyses as a mixture. Anal. Calcd for $C_{13}H_{20}N_2O_6 \cdot {}^1/_4H_2O$: C, 51.22; H, 6.78; N, 9.19. Found: C, 51.5; H, 6.9; N, 8.9. TLC (**4b**), system I, R_f 0.51; system II, R_f 0.44. TLC (**5**), system I, R_f 0.45; system II, R_f 0.41.

***trans*-5-(2-Phenylethenyl)uridine (3e).** 5-Chloromercuriuridine (**1**, 1.59 g, 3.32 mmol), styrene (1.9 mL), and 0.1 M Li_2PdCl_4 in methanol (33.2 mL) were stirred under argon in a 50-mL round-bottom flask for 7 h at room temperature. The mixture was then filtered and the filtrate concentrated to 5 mL. Ethanol (30 mL) was added and the solution treated with solid sodium borohydride (173 mg) in small portions. Filtration and removal of the solvent from the filtrate in vacuo left an oil which was chromatographed on silica gel eluting first with 10% methanol-chloroform (v/v) to remove styrene and then with 18% methanol-chloroform to remove the nucleosides. The fractions showing a blue fluorescent band on TLC (acetone) at R_f 0.48 were combined, and the residue obtained on in vacuo removal of the solvent was recrystallized from water yielding 443.2 mg of **3e** (39%): mp 204–205 °C; ^{1}H NMR (Me_2SO-d_6, internal Me_4Si) δ 3.74 (2 H, m, H_2C-5′), 4.07 (3 H, m, HC-2′, HC-3′, HC-4′), 5.0–5.5 (3 H, 3-OH), 5.88 (1 H, d, J = 3.5 Hz, HC-1′), 6.89 (1 H, d, J = 17 Hz, UC*H*=CHPh), 7.42 (5 H, m, $-C_6H_5$), 7.48 (1 H, d, J = 17 Hz, UCH=*CH*Ph), 8.40 (1 H, s, HC-6); mass spectrum *m/e* (rel abundance) 346 (17, molecular ion), 215 (44, B + 2H), 214 (100, B + H), 143 (66, $PhCH{=}CHC_2HN$), 133 (1.5, ribosyl), 115 (26, PhCH=CHC). Anal. ($C_{17}H_{18}N_2O_6$) C, H, N. UV (H_2O): λ_{max} 309 nm (ϵ 19 100). TLC: system I, R_f 0.47; system II, R_f 0.44.

Methyl *trans*-3-(5-Uridylyl)propenoate (3d). A. From 5-Chloromercuriuridine. 5-Chloromercuriuridine (0.883 g, 1.84 mmol), methyl acrylate (1.0 mL), and 0.1 M Li_2PdCl_4 in methanol (18.4 mL) were combined in a 25-mL round-bottom flask and stirred under argon for 10 h. The mixture was filtered and the precipitate collected, warmed in methanol (30 mL), and refiltered. The combined filtrates were treated with H_2S gas until precipitation of brown HgS was complete, then the solution was filtered and the solvent removed from the filtrate in vacuo. The residue was dissolved in water (4 mL), which was then removed in vacuo. Water (10 mL) was added and the mixture cooled until crystallization of **3d** was complete. Filtration gave 170.5 mg of first crop. Concentration of the mother liquor, followed by further cooling, gave a second crop of 119.1 mg of **3d** (48% combined yield first and second crops): mp 202–204 °C; ^{1}H NMR (TFA) δ 3.97 (3 H, s, $-OCH_3$), 4.2–4.8 (5 H, m, ribose protons), 6.10 (1 H, broad s, HC-1′), 7.09 (1 H, d, J = 16.5 Hz, $-CHCO_2CH_3$), 7.68 (1 H, d, J = 16.5 Hz, $-CH{=}CHCO_2CH_3$), 8.35 (1 H, s, HC-6); mass spectrum *m/e* (rel intensity) 196 (8, B + H), 133 (3, ribosyl), 44 (100, CO_2); UV (H_2O) λ_{max} 300 nm (ϵ 19 900). Anal. ($C_{13}H_{16}N_2O_8$) C, H, N. TLC: system I, R_f 0.41; system II, R_f 0.42.

B. From 5-Iodouridine. 5-Iodouridine (0.230 g, 0.622 mmol), methyl acrylate (0.107 g, 1.245 mmol), triethylamine (0.107 mL, 0.778 mmol), triphenylphosphine (0.0165 g, 0.063 mmol), and palladium acetate (0.007 g, 0.031 mmol) were combined in a 10-mL pear-shaped flask and heated under reflux for 12 h. The resulting gray mass was dissolved in a minimum amount of methanol and after filtration and evaporation of methanol in vacuo gave a white solid. The solid was washed with ethanol to give 108 mg of **3d** (53%, mp 202–204 °C) showing a single spot on TLC identical in R_f (Table I) with the material prepared by method A above. Identity was further established by the ^{1}H NMR and UV spectrum.

5-(4-Hydroxypentyl)uridine (7d) and 5-Pentyluridine (7e). 5-Chloromercuriuridine (0.733 g, 1.61 mmol), 4-penten-2-ol (0.4 mL), and 0.1 M Li_2PdCl_4 in methanol (16.1 mL) were stirred under argon in a 50-mL round-bottom flask for 2 h. The palladium was removed by gravity filtration, the filtrate concentrated to 10 mL, and 10 mL of isopropyl alcohol added followed by $NaBH_4$ (60 mg) in small portions. After 30 min at room temperature the solution was filtered and evaporated to dryness in vacuo three times with 30-mL portions of anhydrous methanol. The residue was dissolved in 25 mL of methanol and 100 mg of Norite and 0.5 mL of 0.1 M Li_2PdCl_4 in methanol were added. The mixture was then stirred under H_2 (30 psig) for 14 h. Filtration and evaporation of methanol in vacuo left a colorless oil which was chromatographed on silica gel (75 g) eluting initially with 15% methanol-chloroform until elution of **7e** was complete and then with 30% methanol-chloroform to elute **7d**. Nucleoside **7d** was further purified by chromatography on Bio-Gel P-2 (66 × 1.8 cm column) eluting with H_2O to give 291.6 mg of **7d** (55%). Although this material is pure by TLC, last traces of inorganic salts can only be removed by recrystallization from ethanol-acetonitrile-diethyl ether (1:3:6) to give fine, white microneedles: mp 174–176 °C; ^{1}H NMR (D_2O) δ 1.16 (3 H, d, J = 6.5 Hz, $-CH_3$), 1.47 (4 H, m, $-CH_2CH_2CH_2CH(OH)$-CH_3), 2.31 (2 H, m, $-CH_2CH_2CH_2CH(OH)CH_3$), 3.90 (2 H, m, H_2C-5′), 4.24 (3 H, m, HC-2′, HC-3′, HC-4′), 5.89 (1 H, d, J = 3 Hz, HC-1′), 7.75 (1 H, s, HC-6); mass spectrum *m/e* (rel intensity) 330 (4, molecular ion), 253 (3), 251 (5), 245 (5), 239 (10), 227 (4), 198 (11), 199 (11), 183 (13), 180 (33), 154 (23), 152 (24), 139 (23), 138 (100); UV (H_2O) 266 nm. Anal. ($C_{14}H_{22}N_2O_7$) C, H, N. TLC: system I, R_f 0.28; system II, R_f 0.16.

Nucleoside **7e**, which showed only a single spot on TLC after the silica gel chromatography, was obtained as a white solid (60.3 mg) by dissolving in 5 mL of water and lyophilizing. Despite apparent high purity the product subsequently underwent transformation to a glass

on standing in a closed flask at room temperature: ^{1}H NMR (D_2O) δ 0.85 and 1.3 (9 H, br multiplets, $-CH_2CH_2CH_2CH_2CH_3$), 2.29 (2 H, m, $-CH_2(CH_2)_3CH_3$), 3.91 (2 H, m, H_2C-5′), 4.28 (3 H, m, HC-2′, HC-3′, HC-4′), 5.93 (1 H, m, HC-1′), 7.76 (1 H, s, HC-6); mass spectrum *m/e* (rel intensity) 314 (5, molecular ion), 183 (43, B + 2H), 182 (68, B + H), 181 (21, B), 133 (16, ribosyl); *m/e* 314.145 (M^+, calcd 314.148). TLC: system I, R_f 0.45; system II, R_f 0.40.

5-(4,5-Dihydroxypentyl)-2′-deoxyuridine (7f). In a 25-mL round-bottom flask were combined 5-mercuri-2′-deoxyuridine (483.0 mg, 1.13 mmol), 1-benzyloxy-4-penten-2-ol (1.08 g, 5.62 mmol), methanol (2 mL), and 0.1 M Li_2PdCl_4 in methanol (10.1 mL). The reaction mixture was stirred for 3 h at room temperature and then filtered. Sodium borohydride (100 mg) was added in 10-mg portions to the filtrate. After hydrogen evolution was complete, the mixture was filtered, the methanol removed from the filtrate in vacuo, and the residue subjected to catalytic hydrogenation in methanol (30 mL), 10% Pd/C (100 mg) under an H_2 atmosphere (16 psig) for 20 h. The mixture was filtered and the residue from in vacuo removal of the methanol was chromatographed on silica gel (50 g) eluting first with acetone to remove less polar impurities and then with 20% ethanol–acetone (v/v) to elute nucleoside **7f.** In this and most other runs the less polar compound (R_f 0.52, acetone eluent on silica gel) was resubjected to catalytic hydrogenation under the conditions described above. The residue from the second catalytic hydrogenation was then combined with nucleoside **7f** from the initial chromatography and rechromatographed on silica gel (50 g) eluting with 10% ethanol–acetone (v/v) to give 0.190 g of purified **7f** as long needles (57%): mp 151–152 °C; ^{1}H NMR δ 1.52 (4 H, m, $-CH_2CH_2CH_2CHCH_2OH$), 2.37 (4 H, overlapping t and dd, $-CH_2CH_2CH_2CHOHCH_2OH$ and H_2C-2′), 3.56 (2 H, m, $-CH_2CH_2CH_2CHOHCH_2OH$), 3.82 (2 H, m, H_2C-5′), 4.04 (1 H, m, HC-3′), 4.49 (1 H, m, HC-4′), 6.28 (1 H, t, J = 6.5 Hz, HC-1′), 7.71 (1 H, s, HC-6); IR (KBr) 1646, 1722 cm^{-1}; mass spectrum *m/e* (rel intensity) 330 (1, molecular ion), 300 (1, MH − CHO(5′)), 213 (3, B), 214 (7, B + 1H), 215 (5, B + 2H), 196 (20, B + H − H_2O), 183 (100, B + H − CH_2OH), 117 (50, sugar); UV (H_2O) 267 nm (ϵ 9100). Anal. ($C_{14}H_{22}N_2O_7$) C, H, N. TLC: system I, R_f 0.20; system II, R_f 0.10.

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References and Notes

(1) R. H. Hall, "The Modified Nucleosides in Nucleic Acids", Colombia University Press, New York, N.Y., 1971, pp 23–25, 181, and 286.
(2) D. B. Dunn and M. D. M. Trigg, *Biochem. Soc. Trans.*, **3**, 656 (1975).
(3) L. Baczynskyj, K. Biemann, and R. H. Hall, *Science*, **159**, 1481 (1968).
(4) J. A. Carbon, H. David, and M. H. Studier, *Science*, **161**, 1146 (1968).
(5) (a) J. Marmur, C. Brandon, S. Neubort, E. Ehrlich, M. Mandel, and J. Konvicka, *Nature (London), New Biol.*, **239**, 68 (1972); (b) C. Brandon, P. M. Gallop, J. Marmur, H. Hayashi, and K. Nakanishi, *ibid.*, **239**, 70 (1972).
(6) M. R. Leob and S. S. Cohen, *J. Biol. Chem.*, **234**, 364 (1959).
(7) (a) R. G. Kallen, M. Simon, and J. Marmur, *J. Mol. Biol.*, **5**, 248 (1962); (b) D. H. Roscoe and R. G. Tucker, *Biochem. Biophys. Res. Commun.*, **16**, 106–110 (1964).
(8) A. M. B. Kropinski, R. J. Bose, and R. A. J. Warren, *Biochemistry*, **12**, 151 (1973).
(9) (a) D. Shugar in "Virus-Cell Interactions and Viral Antimetabolites", D. Shugar, Ed., Academic Press, New York, N.Y., 1972, pp 193–107; (b) D. Shugar, *FEBS Lett.*, **40**, S48 (1974).
(10) M. Swierkowski and D. Shugar, *J. Med. Chem.*, **12**, 533 (1969).
(11) W. H. Prusoff and B. Goz in "Antineoplastic and Immunosuppressive Agent'", Vol. 2, A. C. Sartorelli and D. G. Johns, Ed., Springer-Verlag, West Berlin, 1975, p 272; W. H. Prusoff and B. Goz, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **32**, 1679 (1973).
(12) E. De Clercq and D. Shugar, *Biochem. Pharmacol.*, **24**, 1073–1078 (1975).
(13) (a) R. M. K. Dale, D. C. Livingston, and D. C. Ward, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 2238 (1973); (b) R. M. K. Dale, E. Martin, D. C. Livingston, and D. C. Ward, *Biochemistry*, **14**, 2447 (1975); (c) R. M. K. Dale and D. C. Ward, *ibid.*, **14**, 2458 (1975).
(14) R. L. Barfknecht, R. A. Heut-Rose, A. Kampf, and M. P. Mertes, *J. Am. Chem. Soc.*, **98**, 5041 (1976).
(15) T. K. Bradshaw and D. W. Hutchinson, *Chem. Soc. Rev.*, **6**, 43–62 (1977).
(16) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors", Wiley, New York, N.Y., 1967, p 94.
(17) A. Kampf, R. L. Barfknecht, P. J. Shaffer, S. Osaki, and M. P. Mertes, *J. Med. Chem.*, **19**, 903 (1976).
(18) K. K. Gauri, Fr. M. 7652; *Chem. Abstr.*, **76**, 141287e (1972).
(19) M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **33**, 2822 (1968).
(20) A. Szabolcs, J. Sági, and L. Ötvös, *J. Carbohydr. Nucleosides Nucleotides*, **2**, 197–211 (1975).
(21) R. A. Sharma and M. Bobek, *J. Org. Chem.*, **40**, 2377 (1975).
(22) P. Langen and D. Barwolff, *Biochem. Pharmacol.*, **24**, 1907–1910 (1975).
(23) J. Perman, R. A. Sharma, and M. Bobek, *Tetrahedron Lett.*, 2427–2430 (1976).
(24) D. E. Bergstrom and J. L. Ruth, *J. Carbohydr. Nucleosides Nucleotides*, **4**, 257 (1977).
(25) D. E. Bergstrom and J. L. Ruth, *J. Am. Chem. Soc.*, **98**, 1587 (1976).
(26) R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5518, 5526, 5531, 5535 (1968).
(27) J. Shapira, *J. Org. Chem.*, **27**, 1918 (1962).
(28) The lability of 5-vinyluracil to polymerization has previously been observed: A. S. Jones and R. T. Walker, *Nucleic Acids Res., Spec. Publ. 1*, s1 (1975).
(29) The product showed a single spot on TLC and an ^{1}H NMR spectrum identical with that of analytically pure material, but is contaminated with 5–10% lithium chloride which could be removed by silica gel chromatography eluting with methanol–chloroform.
(30) J. L. Ruth and D. E. Bergstrom, *J. Org. Chem.*, **43**, 2870 (1978).
(31) H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, **96**, 1133 (1974).
(32) A. J. Jones, D. M. Grant, M. W. Winkley, and R. K. Robins, *J. Phys. Chem.*, **74**, 2684 (1970); *J. Am. Chem. Soc.*, **92**, 4079 (1970).
(33) E. Breitmaier, G. Jung, and W. Voelter, *Chimia*, **26**, 136 (1972).
(34) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists", Wiley, New York, N.Y., 1972.
(35) Although the chloromercurinucleosides **1** and **2** were generally used in the synthesis described, a polymeric C-5 to N-3 linked mercurinucleoside (ref 24) was utilized in a few reactions without apparently changing the outcome. This species is referred to as 5-mercuri-2′-deoxyuridine throughout.
(36) R. F. Heck, *J. Am. Chem. Soc.*, **93**, 6896 (1971).
(37) F. H. A. Rummens and J. W. de Haan, *Org. Magn. Reson.*, **2**, 351–355 (1970).
(38) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "High Resolution NMR Spectra Catalog", Vol. 2, 1963, Spectrum No. 232.
(39) J. R. Geigy, British Patent 833 573 (April 27, 1960); *Chem. Abstr.*, **55**, 1652*h* (1961).
(40) L. Palfary and S. Sabetay, *Bull. Soc. Chim. Fr.*, **4**, 950 (1937).
(41) $Rh(CH_3)I_2(PPH_3)_2$ was generously supplied by Richard C. Larock, who has found it to be an effective reagent in HMPA for replacing the mercury of arylmercurials by a methyl group.
(42) R. F. Heck, *J. Am. Chem. Soc.*, **94**, 2712 (1972).
(43) H. A. Dieck and R. F. Heck, *J. Organomet. Chem.*, **93**, 259 (1975).
(44) R. F. Heck, *J. Am. Chem. Soc.*, **91**, 6707 (1969).
(45) F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials", McGraw-Hill, New York, N.Y., 1968.
(46) R. F. Heck, *Ann. N.Y. Acad. Sci.*, **295**, 215 (1977).
(47) R. C. Larock and M. A. Mitchell, *J. Am. Chem. Soc.*, **100**, 180 (1978).
(48) D. F. Hunt and G. T. Rodeheaver, *Tetrahedron Lett.*, 3595 (1972).
(49) E. Kent Barefield, *J. Chem. Educ.*, **50**, 697 (1973).
(50) The mass spectra of **7c** obtained by the catalytic hydrogenation of 5-allyluridine and the mixture of **7c** and **8a** were identical.
(51) These δ values represent a correction of values reported earlier (ref. 30) for nucleoside **3b**.