Palladium-Catalyzed Coupling Reactions of Uracil Nucleosides and Nucleotides

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Abstract: A new method is described for the facile alkylation of uracil nucleotides. Treatment of the unprotected nucleotide with mercuric acetate followed by the addition of styrene or ring-substituted styrenes and lithium tetrachloropalladate affords the C-5-*trans*-styryl derivatives. The coupling reactions using nucleosides or nucleotides proceed in moderate to good yield, can be run in protic solvents, are not adversely affected by the presence of the phosphate group or sugar hydroxyls, and are compatible with nitro, amino, and azido substitution of the phenyl ring in styrene.

Chemical modification of nucleic acids has been a valuable tool for the structural elucidation and the analysis of physicochemical properties of these important biological materials. A classical example, the chemical modification of viral ribonucleic acid by dimethyl sulfate or *N*-methyl-*N'*-nitrosoguanidine, was useful in the identification of available nucleophilic sites on the RNA bases.[1] More recently, alkylation of nucleic acids by the metabolite of benzo[*a*]pyrene was a key experiment in addressing the mechanism of carcinogenesis.[2]

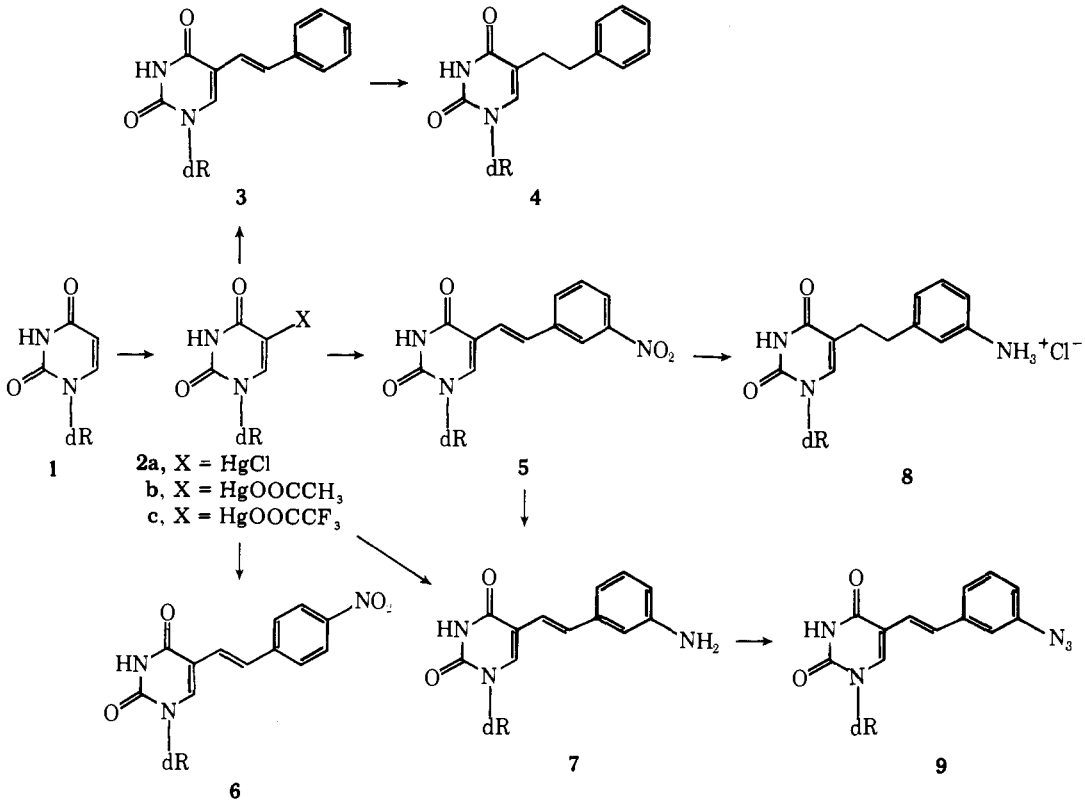
Principally because of the polar nature of nucleic acids, chemical reactivity is limited to those sites that can be modified by reactions in protic solvents. Under these conditions electrophilic reagents most commonly interact with nucleophilic sites on nucleic acids to give the N- or O-alkylated products. Modification of nucleic acids to give alkylation at carbon for the most part is limited to photochemical reactions.

Bergstrom and Ruth[3] have described a unique reaction leading to carbon alkylation of nucleosides via the intermediacy of an organopalladium complex of the pyrimidine base. Palladium-catalyzed reactions involving the addition of an arylpalladium complex to an olefin have been reviewed by Heck.[4]

We have explored the application of this reaction to uracil nucleosides and nucleotides and observed that carbon alkylation of C-5 of the uracil ring in the ribo- and deoxyribonucleosides and nucleotides proceeds in high yields in aqueous-alcoholic solution. These results,[5] together with those of Bergstrom[3,6] and co-workers using acrylate esters, show that addition to the olefin followed by elimination gives the terminally substituted trans olefin product in high yields. These preliminary findings suggest that the reaction holds promise as a practical and facile method for the selective chemical modification of polynucleotides by formation of carbon-alkylated products at C-5 of the pyrimidine bases in polynucleotides.

Impetus for this investigation was provided by the recently demonstrated utility of the palladium-catalyzed coupling reaction between mercurinucleosides and olefins.[3] When 5-chloromercuri-2'-deoxyuridine[7] (**2a**, Scheme I) was suspended in methanol and treated with styrene and lithium tetrachlo-

Scheme I[a]



[a] dR = 2'-deoxyribose.

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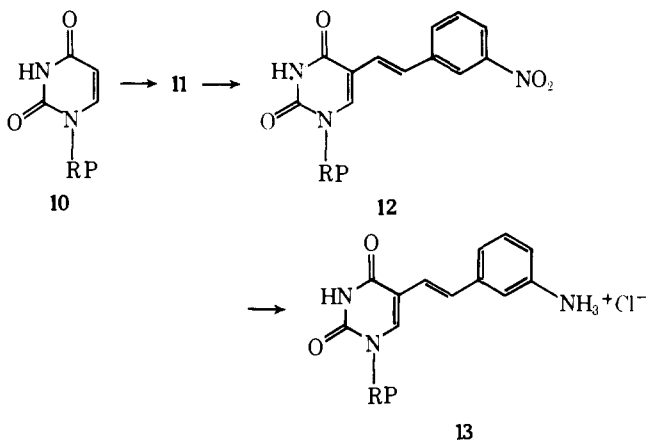
Scheme II[a]



10 12 13

[a] RP = ribose 5′-phosphate.

ropalladate at reflux, precipitation of Pd^0 resulted. After removal of the palladium and mercury salts as sulfides, purification of 5(*E*)-styryl 2′-deoxyuridine (**3**) was accomplished by resolution on silica gel and recrystallization from 1-octanol in 57% yield. The ^1H NMR data indicated that the product was exclusively trans, as expected, since the vinylic protons at δ 7.38 and 6.86 each had a coupling constant of J = 16.5 Hz. The trans product (**3**) is expected according to the results of Dieck and Heck[8] formulated as syn addition of the organopalladium intermediate to the olefin followed by syn elimination of hydridopalladium chloride to give the product from alkylation of the least substituted carbon of the olefin.

The reduced nucleoside derivative (**4**) was obtained by an alternative reaction workup of the coupling reaction when the reaction mixture of **3** was treated with sodium borohydride and the crude filtrate further reduced by hydrogenation using palladium on carbon to give 5-(2-phenylethyl)-2′-deoxyuridine (**4**).

An electronic effect was observed in the arylation of styrene compared to nitrostyrene.[9] The conversion of **2a** to the 3-nitrostyryl nucleoside (**5**) proceeded in 50% recrystallized yield. However, TLC analysis of the reaction of **2a** with 4-nitrostyrene revealed a low (less than 2%) yield of **6** that was initially thought to be due to an electronic effect[5] but in more recent studies appears to be a result of limited solubility of 4-nitrostyrene.

An improvement in yield, together with a more convenient procedure that obviated isolation of the intermediate mercurinucleoside, was observed when the nucleoside **1** was converted to the acetoxymercuri derivative[7b] (**2b**); treatment with 3-nitrostyrene and lithium tetrachloropalladate gave the product **5** in 62% yield. 4-Nitrostyrene was utilized in the same procedure affording an 11% yield of **6**. Utilization of mercuric trifluoroacetate instead of mercuric acetate allowed the use of milder conditions without a substantial loss in yield.

Heck[10] has shown that catalytic amounts of palladium(II) can be used to effect the coupling reaction when the product, palladium(0), is reoxidized by cupric chloride. Using 0.1 equiv of lithium tetrachloropalladate and 4 equiv of cupric chloride, both **3** and **5** were prepared from **2a** in 47 and 49% yield. The insignificant yield reduction using the recycling oxidant, copper(II), offers a considerable economic alternative.

Palladium-catalyzed coupling reactions are remarkably tolerant of a wide variety of functional groups.[4,9,11] Plevyak and Heck[12] noted that amino, formyl, and carboxyl substituents were accommodated in this reaction without affecting yields. The direct coupling reaction of **2b** with 3-aminostyrene[13] in the presence of lithium tetrachloropalladate in tetrahydrofuran demonstrated the applicability of the reaction to olefinic systems in the presence of free amino groups. The reaction afforded the product **7** (30%) identified by elemental analysis and the appearance of the C-6 and olefinic protons in the ^1H NMR spectrum at δ 8.25, 7.33, and 6.87, respectively. The structure was further confirmed by a *m/e* peak of 228 (heterocyclic base) in the mass spectrum, a positive ninhydrin test on TLC, and a broad ultraviolet absorption maximum at 288–300 nm in methanol and base and a bathochromic shift to 312 nm in acid.

The amino nucleoside **7** also was prepared by reduction of the corresponding nitro nucleoside **5** with hydrazine in the presence of a catalytic amount of Raney nickel. When an excess of hydrazine or hydrogenation using platinum catalyst was applied to the nitrostyryl nucleoside **5**, nonselective reduction of both the nitro group and the double bond afforded 5-(3-aminophenylethyl)-2′-deoxyuridine (**8**) in high yield (83%).

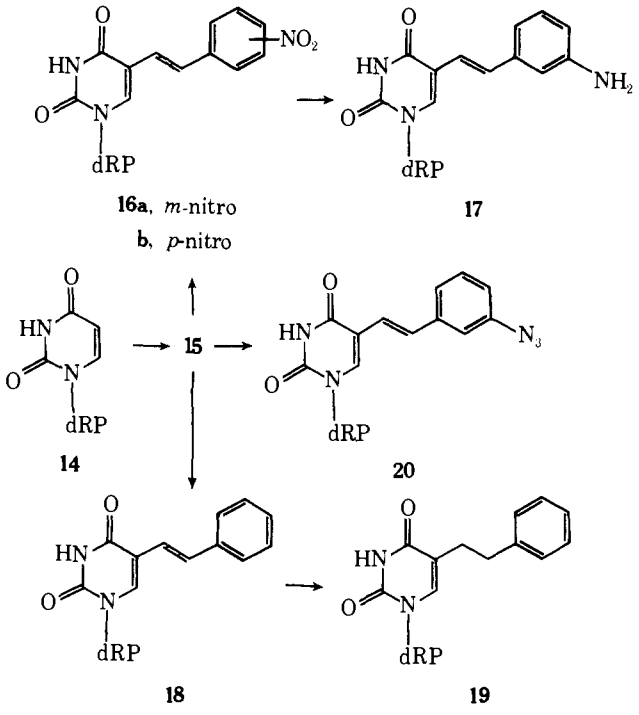
A potentially useful nucleoside or nucleotide derivative for structural studies is one containing a photochemically active function. Aryl azides are chemically stable functions that give nitrenes after photoactivation; such ATP analogues are useful photoaffinity labels for biochemical studies on the enzyme ATPase.[14] An arylazido group covalently bonded to pyrimidine bases in nucleic acids would be a useful photochemically active probe of RNA or DNA solution structure. Conversion of the aminostyryl nucleoside **7** to 5(*E*)-(3-azidostyryl)-2′-deoxyuridine (**9**) was accomplished by diazotization of the sulfate salt of **7** using sodium nitrite followed by displacement with azide ion. In addition to elemental analysis the product **9** was characterized by the azide stretching absorption in the infrared and by the electron impact mass spectrum affording the intact heterocyclic ring from glycosidic bond cleavage, *m/e* 254, and that fragment minus N_2 (*m/e* 226). The ^1H NMR spectrum of **9** showed a complex pattern in the aromatic region which was assigned to δ 6.79 for the uracil CH and δ 7.39 for the phenyl CH olefinic protons. Two unique high-intensity absorption peaks at 312 and 249 nm were observed in the ultraviolet spectrum of **9**.

Application of the palladium-catalyzed coupling reaction to the C-5 alkylation of pyrimidine nucleotides was explored using uridine 5′-phosphate and its 2′-deoxy derivative. Since it was found that purification of the mercurinucleoside was unnecessary in the model reactions using nucleosides, and further that the presence of acetate did not affect the yield, the acetoxymercuri derivative **11** of uridine 5′-phosphate (**10**) was coupled with 3-nitrostyrene. TLC analysis revealed the reaction to be complete in 30 min; after the usual workup to remove the heavy metal salts, the product **12** was collected in 82% recrystallized yield. Characterization of the product included elemental analysis, a positive phosphate test, ultraviolet absorption matching that of the nucleoside **5**, and an electron impact mass spectrum of **12** showing the heterocyclic fragment (5-(3-nitrostyryl)uracil, *m/e* 259) which results from fragmentation of the glycosidic bond. Further structural verification was obtained when the nitrostyryl nucleotide **12** was converted to the corresponding amino derivative **13** by reduction by hydrazine in the presence of W-2 Raney nickel.

The olefinic protons of 5-(3-nitrostyryl)uridine 5′-phosphate (**12**) gave the typical AB coupled pattern with coupling constants of 16 Hz. The proton on the carbon α to the uracil ring is assigned a chemical shift of δ 6.52, whereas the proton on the carbon adjacent to the nitrophenyl group has a chemical shift of δ 6.95. This assignment is based on the greater deshielding effect exerted on the former proton when the uracil ring is in the ionic form; the NMR spectra of compound **12** in NaOD had olefinic resonance signals at δ 6.82 and 7.07. The former signal is a 0.3-ppm chemical shift from that of the neutral compound.

The ^{13}C NMR assignments[15] are listed in Table I. Significant deshielding is noted in comparing the ^{13}C NMR spectra of a neutral and basic solution of **12**. The greatest shift is ob-

Scheme III[a]



[a] dRP = 2′-deoxyribose 5′-phosphate.

served for carbonyl carbons 2 and 4 of the uracil ring; the respective assignments for the neutral molecule at 152.74 and 165.41 ppm appear at 161.14 and 176.67 ppm in the basic solution. Considerably less effect from ionization of the uracil ring is observed for the chemical shifts of the uracil ring C-5 and the adjacent olefinic carbon.

For studies using the 2′-deoxy nucleotide series, the phosphate **14** (Scheme III) was converted to the acetoxymercuri derivative **15**; the ^{1}H NMR of **15** showed a singlet resonance signal for the C6-H at δ 7.84 and the anomeric C1′-H as a triplet at δ 6.32. The coupling reaction with 3-nitrostyrene afforded 5(*E*)-(3-nitrostyryl)-2′-deoxyuridine 5′-phosphate (**16a**) in 66% yield. The coupling reaction of 4-nitrostyrene with the nucleoside afforded a low yield (11%) of the product **6**. Since the nucleotide coupling reaction of **15** with 4-nitrostyrene gave a 59% yield of **16b** it would appear that the electronic effect[5] is not a significant factor in these reactions. Reduction of **16a** with a slight excess of hydrazine in the presence of a catalytic amount of W-2 Raney nickel gave the aminostyryl nucleotide **17**. The palladium-catalyzed coupling reaction of the deoxynucleotide **15** with styrene in the mixed solvent water-methanol-tetrahydrofuran (1:0.8:1.6 ratio) yielded 50% of 5(*E*)-(styryl)-2′-deoxyuridine 5′-phosphate (**18**). Reduction of **18** to 5-(2-phenylethyl)-2′-deoxyuridine 5′-phosphate (**19**) was accomplished by hydrogenation using palladium on carbon.

The substitution of 3-azidostyrene at C-5 of 2′-deoxyuridine 5′-phosphate was attempted to demonstrate the versatility of the reaction for the direct introduction of a photochemically active probe. The starting olefin, 3-azidostyrene, was prepared by diazotization of 3-aminostyrene followed by displacement with sodium azide. Sundberg and co-workers[16] followed this route to 2-azidostyrene. Diazotization of 3-aminostyrene is reported to give a triazine.[17] However, using an excess of sodium nitrite and treatment of the cold diazo compound with azide we did not observe the reported triazine Characterization of 3-azidostyrene was supported by the mass spectrum (*m/e* 145, molecular ion; 117, molecular ion − N_2), intense absorption in the ultraviolet at 237 nm with the arylazido band as a shoulder at 300 nm,[18] the azide stretching frequency in the infrared, and the ^{1}H NMR spectra. The NMR shows a significant downfield shift for the olefinic protons compared to the same signals in 3-aminostyrene.

The acetoxymercuri derivative **15** was coupled with 3-azidostyrene to give 5(*E*)-(3-azidostyrene)-2′-deoxyuridine 5′-phosphate (**20**). Evidence for the structure was derived from elemental analysis and the infrared, ultraviolet, and ^{1}H NMR spectra.

Table I. ^{13}C NMR Spectral Assignments for 5(*E*)-(3-Nitrostyryl)-uridine 5′-Phosphate (**12**)

carbon[a]	neutral sol[b]	basic soln[c]
C-2	152.74	161.14
C-4	165.41	176.67
C-5	114.26	115.08
C-6	141.29	141.88
C-1′	91.08	92.54
C-2′[d]	76.66	76.31
C-3′[d]	72.46	73.21
C-4′	85.83	85.83
C-5′	66.62	66.85
C-1″	140.71	140.59
C-2″, C-4″ } UC=	123.54, 124.07, 124.33	123.13, 124.07 126.99
C-3″	150.23	150.46
C-5″	129.56	128.10
ARC=	134.75	134.87

[a] Shifts are given in parts per million relative to internal DDS; C refers to the uracil ring, C′ to the sugar, and C″ to the aromatic carbons. [b] Compound **12** at 0.1 M concentration in 0.1 M sodium acetate in D_2O was used in this experiment. [c] Compound **12** (58.6 mg, 0.12 mmol) was dissolved in 0.5 mL of 1.2 M NaOH/D_2O and this solution diluted with D_2O. [d] The assignments for these carbons are based on the corrections to earlier work by Mantsch, H. H.; Smith, I. C. P. *Biochem. Biophys. Res. Commun.* **1972**, *46*, 808-815.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were measured with a Beckman IR-33, UV spectra with a Cary Model 219 or Perkin-Elmer Model 554 recording spectrophotometer, ^{1}H NMR spectra with Varian Model EM-360 or T-60 or Perkin-Elmer R-32, and ^{13}C NMR on a JEOL FX-100 spectrometer by the Colorado State Regional NMR Center Staff. Microanalyses were obtained from a Hewlett-Packard 185B and mass spectra from a Varian CH5 spectrometer. DEAE cellulose was the product of Whatman Biochemical Ltd.; 2′-deoxyuridine (B grade) and 2′-deoxyuridine 5′-phosphate were purchased from Calbiochem, uridine 5′-phosphate and 3-nitrostyrene from Aldrich, and palladium chloride from Ventron.

A 0.1 M solution of lithium tetrachloropalladate was prepared by stirring palladium chloride (1.77 g, 10 mmol) and lithium chloride (0.85 g, 20 mmol) in 100 mL of anhydrous methanol overnight at room temperature.

5(*E*)-Styryl-2′-deoxyuridine (3). Method A. A solution of 0.1 M lithium tetrachloropalladate (11 mL) was added with stirring to a suspension of 5-chloromercuri-2′-deoxyuridine[7d] (**2a**, 463 mg, 1 mmol) and styrene (310 mg, 3 mmol) in 11 mL of methanol. After refluxing for 12 h the mixture was saturated with hydrogen sulfide gas and filtered through Celite, and the filtrate evaporated. The mixture was resolved on a silica column (3 × 40 cm) using 0–10% methanol in chloroform as eluent to give 306 mg of white solid. Recrystallization from 1-octanol gave a yield of 175 mg (57%) of compound **3**: mp 195–196 °C; mass spectrum *m/e* 330 (molecular ion), 214 (heterocyclic base), 143, 117; UV (H_2O) λ_{max} 305 (ϵ 17 600), λ_{min} 238 (6000); ^{1}H NMR (CD_3COOD) δ 8.2 (s, 1 H, C-6), 7.63–6.92 (m, 5 H, aromatic), 7.38 (d, 1 H, J = 16.5 Hz, PhCH=), 6.86 (d, 1 H, J = 16.5 Hz, U—CH=), 6.31 (t, 1 H, J = 6 Hz, C-1′).

Anal. ($C_{17}H_{18}N_2O_5$, 330.33) C, H, N.

5(*E*)-Styryl-2′-deoxyuridine (**3**) also was prepared in 47% yield by method A with the exception that a catalytic amount of lithium tetrachloropalladate (26 mg, 0.1 mmol) was used together with cupric chloride (538 mg, 4 mmol).

Method B. A solution of 2′-deoxyuridine (**1**, 228 mg, 1 mmol) and mercuric acetate (319 mg, 1 mmol) in 10 mL of water was heated with stirring at 60 °C for 5 hr. After removal of acetic acid formed in the reaction and water in vacuo, the resulting white solid was suspended in 11 mL of methanol and stirred with styrene (0.4 mL, 3.5 mmol) and 11 mL of 0.1 M lithium tetrachloropalladate in methanol at reflux for 12 h. Workup was identical with method A and gave 148 mg (45%) of compound **3** after recrystallization from 1-octanol.

5-(2-Phenylethyl)-2′-deoxyuridine (4). Method A. A 0.1 M solution of lithium tetrachloropalladate (75 mL) was added to a suspension of 5-chloromercuri-2′-deoxyuridine (**2a**, 3.05 g, 6.59 mmol) and styrene (2.04 g, 11 mmol) in 75 mL of methanol with stirring and the mixture refluxed overnight. After the black precipitate was filtered, the filtrate was treated with sodium borohydride (200 mg, 5.3 mmol) to reduce the soluble mercury and palladium salts and the mixture filtered through Celite. The filtrate was added slowly to prewetted 10% Pd/C (100 mg) and stirred at room temperature under 1 atm hydrogen gas for 20 h when analysis by thin layer chromatography (17:3 ethyl acetate–methanol) showed that all of the 5-styryl-2′-deoxyuridine was gone. After filtration through Celite and evaporation, the residue was resolved on silica gel using methanol in chloroform (0–10%) as eluent. The appropriate fractions were combined and evaporated to yield 1.24 g (57.8%) of compound **4**: mass spectrum *m/e* 332 (molecular ion), 216 (heterocyclic base), 117; IR (KBr) 2920, 1690, 1675, 1650 cm^{-1}; UV (0.1 N HCl) λ_{max} 266, λ_{min} 232 nm; ^1H NMR (D_2O, CD_3OD) δ 7.39 (1 H, s, C-6), 7.33–6.95 (5 H, m, aromatic), no vinylic protons, 6.07 (1 H, t, J = 5.4 Hz, C-1′).

Anal. ($C_{17}H_{20}N_2O_5 \cdot CH_3OH$, 364.4) C, H, N.

Method B. A solution of 5(*E*)-styryl-2′-deoxyuridine (**3**, 103 mg, 0.32 mmol) in 40 mL of methanol was added to prewetted 5% palladium on carbon (100 mg) and stirred under 1 atm of hydrogen gas at room temperature for 24 h. After uptake of hydrogen gas was complete the mixture was filtered through Celite, evaporated, and resolved on a silica gel column using methanol in chloroform (0–10%) as eluent. The appropriate fractions were combined and evaporated to yield 93 mg (89%) of compound **4**, which was identical with the material obtained by method A.

5(*E*)-(3-Nitrostyryl)-2′-deoxyuridine (5). Method A. A solution of 0.1 M lithium tetrachloropalladate (11 mL) was added with stirring to a suspension of 5-chloromercuri-2′-deoxyuridine (**2a**, 463 mg, 1 mmol) and 3-nitrostyrene (450 mg, 3 mmol) in 11 mL of methanol. After refluxing overnight the mixture was saturated with hydrogen sulfide gas and filtered through Celite and the filtrate evaporated. The mixture was resolved on a silica gel column (3 × 40 cm) using 0–10% methanol in chloroform as eluent and recrystallized from methanol to give 189 mg (50%) of compound **5**: mp 211–212 °C; mass spectrum *m/e* 259 (heterocyclic base), 188, 142, 117; UV (H_2O) λ_{max} 298 nm (ϵ 21 500), λ_{min} 232 (10 000); (0.1 N HCl) λ_{max} 298 nm (ϵ 22 000), λ_{min} 229 (10 500); (0.1 N NaOH) λ_{max} 306 nm (ϵ 22 000), λ_{min} 242 (12 500); IR (KBr) 1690, 1520, 1345, 795, 745, 720 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 8.44 (s, 1 H, C-6), 8.2–7.5 (m, 4 H, aromatic), 7.60 (d, 1 H, J = 16 Hz, PhCH=), 7.11 (d, 1 H, J = 16 Hz, UCH=), 6.37 (t, 1 H, J = 6.2 Hz, C-1′).

Anal. ($C_{17}H_{17}N_3O_7$, 375.33) C, H, N.

5(*E*)-(3-Nitrostyryl)-2′-deoxyuridine (**5**) also was prepared in 49% yield by method A with the exceptions that a catalytic quantity of lithium tetrachloropalladate (26 mg, 0.1 mmol) together with cupric chloride (538 mg, 4 mmol) were used.

Method B. A solution of 2′-deoxyuridine (**1**, 228 mg, 1 mmol) and mercuric acetate (319 mg, 1 mmol) in 10 mL of water was heated with stirring at 60 °C for 5 h. After removal of acetic acid formed in the reaction and water in vacuo, the white solid residue was suspended in 11 mL of methanol and stirred with 3-nitrostyrene (450 mg, 3 mmol) and 11 mL of 0.1 M lithium tetrachloropalladate in methanol at reflux for 12 h. Workup was identical with that of method A and gave 234 mg (62%) of compound **5**.

Method C. A solution of 2′-deoxyuridine (**1**, 228 mg, 1 mmol) and mercuric trifluoroacetate (427 mg, 1 mmol) in 10 mL of tetrahydrofuran was stirred at room temperature until 2′-deoxyuridine was no longer visible on TLC (8 h). After the reaction mixture was cooled to −30 °C, 3-nitrostyrene (450 mg, 3 mmol) and 11 mL of 0.1 M lithium tetrachloropalladate in methanol were added and the reaction mixture was refluxed overnight. Workup was identical with that of method A and gave 194 mg (52%) of compound **5**.

Method D. A 0.1 M solution of lithium tetrachloropalladate (60 mL) in methanol was added to a suspension of **2b** (2.5 g, 5.15 mmol) and 3-nitrostyrene (2.4 g, 16.4 mmol) in 250 mL of tetrahydrofuran. After refluxing for 6 h, the reaction mixture was cooled, saturated with hydrogen sulfide gas, and filtered through Celite and the filtrate evaporated. Resolution by medium-pressure liquid chromatography on silica gel with methanol (5%) in chloroform as eluent followed by recrystallization from a methanol–chloroform solution gave 1.55 g (80%) of compound **5**.

5(*E*)-(4-Nitrostyryl)-2′-deoxyuridine (6). A solution of 2′-deoxyuridine (**1**, 228 mg, 1 mmol) and mercuric acetate (319 mg, 1 mmol) in 10 mL of water was heated with stirring at 60 °C for 5 h. After removal of acetic acid formed in the reaction and water in vacuo, the white residue was suspended in 11 mL of methanol and stirred with 4-nitrostyrene (450 mg, 3 mmol) and 11 mL of 0.1 M lithium tetrachloropalladate in methanol at 60 °C overnight. The mixture was cooled to room temperature, saturated with hydrogen sulfide gas, and filtered through Celite, and the volume of the filtrate reduced. The solution deposited crystals of **6** which were collected by filtration. The filtrate was evaporated and resolved on a silica column (3 × 40 cm) using 0–10% methanol in chloroform as eluent and the resulting residue recrystallized from methanol to give a combined yield of 40 mg of yellow-orange crystals (11%) of compound **6**: mp 230–236 °C; mass spectrum *m/e* 375 (molecular ion), 259 (base), 188, 142, 117; UV (H_2O) λ_{max} 358 nm (ϵ 16 000), λ_{min} 283 (8000); (0.1 N HCl) λ_{max} 360 nm (ϵ 17 500), λ_{min} 285 (ϵ 8500); (0.1 N NaOH) λ_{max} 376 nm (ϵ 17 500), λ_{min} 298 (7000); IR (KBr) 1715, 1670, 1595, 1505, 1350, 955 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 8.33 (s, 1 H, C-6), 8.23 (d, 2 H, J = 9 Hz, aromatic), 7.74 (d, 2 H, J = 9 Hz, aromatic), 7.60 (d, 1 H, J = 16 Hz, PhCH=), 7.21 (d, 1 H, J = 16 Hz, UCH=), 6.20 (t, 1 H, J = 7 Hz, C-1′).

Anal. ($C_{17}H_{17}N_3O_7$, 375.33) C, H, N.

3-Aminostyrene. A suspension of 3-nitrostyrene (9.8 g, 65.7 mmol) in 20 mL of ethanol and 40 mL of hydrochloric acid was treated with a stannous chloride hydrate solution[19] (44.5 g in 50 mL of ethanol) with vigorous stirring at room temperature. The reaction mixture immediately turned clear and was stirred for an additional 4 h, after which time it was neutralized with sodium hydroxide solution. After filtration the solution was extracted with ethyl ether and separated, and the ether layer dried and treated with hydrochloric acid to obtain 3-aminostyrene hydrochloride[13] in 86% yield: mass spectrum *m/e* 120 (molecular ion + 1), 119 (molecular ion); UV (MeOH) λ_{max} 239, λ_{min} 218 nm; ^1H NMR (neat) δ 6.2 (2 dd, 1 H, PhCH, J_{cis} = 10, J_{trans} = 17 Hz), 5.12 (dd, 1 H, trans PhC=CH, J_{cis} = 10, $J_{geminal}$ = 2 Hz), 4.65 (dd, 1 H, cis PhC=CH, J_{trans} = 17, $J_{geminal}$ = 2 Hz).

5(*E*)-(3-Aminostyryl)-2′-deoxyuridine (7). Method A. A 0.274 M solution of lithium tetrachloropalladate (15 mL) in methanol was added with stirring to a suspension of the mercurinucleoside **2b** (2 g, 4.1 mmol) in 200 mL of tetrahydrofuran, followed by an additional 50 mL of methanol. After the reaction mixture was heated to reflux a solution of 3-aminostyrene (1.8 g, 16 mmol) in 100 mL of tetrahydrofuran was added slowly. After 9 h at reflux the solution was cooled to 25 °C, saturated with hydrogen sulfide gas, and filtered through Celite and the filtrate evaporated. The residue was crystallized twice from an ethanol–chloroform solution and further purified by preparative thin layer chromatography on 2-mm silica gel plates eluted with methanol (15%) in chloroform to give a 30% yield of pure, brown, crystalline material (**7**): mp 133–135 °C; mass spectrum *m/e* 345 (molecular ion), 229 (heterocyclic base), 136, 117; UV (MeOH) λ_{max} 300 nm (ϵ 12 500), 288 (13 000), λ_{min} 254 (10 500); (0.1 N HCl) λ_{max} 312 nm (ϵ 15 500), λ_{min} 231 (5000); IR (KBr) 3550, 3460, 3220, 1700, 1685 cm^{-1}; ^1H NMR (CD_3OD) δ 8.25 (s, 1 H, C-6), 7.33 (d, 1 H, J = 17 Hz, PhCH=), 6.87 (d, 1 H, J = 17 Hz, UCH=), 6.32 (t, 1 H, C-1′); (CD_3OD/NaOD) δ 7.18 (d, 1 H, J = 17 Hz, PhCH=), 6.84 (d, 1 H, J = 17 Hz, UCH=).

Anal. ($C_{17}H_{19}N_3O_5 \cdot 0.75\ H_2O$, 345,34) C, H, N.

Method B. A solution of hydrazine hydrate (0.7 g, 14 mmol) followed by a catalytic amount of W2 Raney nickel was added at 25 °C to a solution of compound **5** (2.6 g, 6.93 mmol) in 50 mL of methanol. To prevent overreduction the reaction was followed by thin layer chromatography on silica gel (methanol (12%) in chloroform as eluent) and terminated prior to completion by filtration through Celite. After evaporation of the filtrate, the crude product was resolved on a silica gel column with methanol (12%) in chloroform as eluent to give compound **7** in 67% yield.

5-[2-(3-Aminophenyl)ethyl]-2′-deoxyuridine Hydrochloride (8). A solution of compound **5** (0.5 g, 1.33 mmol) in 15 mL of acetic acid was added to a suspension of platinum oxide (0.14 g, 0.66 mmol) in 15 mL

of acetic acid which was previously saturated with hydrogen gas. After stirring under hydrogen gas at room temperature and atmospheric pressure until uptake of hydrogen ceased, the solution was filtered through activated charcoal and Celite. The filtrate was acidified with 2 mL of hydrochloric acid, the solution was concentrated in vacuo, and the reaction mixture was resolved by medium-pressure liquid chromatography on silica gel with methanol (5%) in chloroform as eluent to give 420 mg (83%) of compound **8**: mp 208–211 °C; mass spectrum *m/e* 347 (molecular ion); UV (MeOH) λ_{max} 266 nm (ϵ 8800), λ_{min} 240; IR (KBr) 3400, 3350, 2580, 2300, 2050, 1680, 1650 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 7.50 (s, 1 H, C-6), 7.12–6.07 (m, 5 H, aromatic, C-1′), 2.60 (s, 4 H, reduced double bond).

Anal. ($C_{17}H_{28}N_3O_5Cl$, 389.87) C, H, N.

5(*E*)-(3-Azidostyryl)-2′-deoxyuridine (9). To 10 mL of a cooled, aqueous solution of 5(*E*)-(3-aminostyryl)-2′-deoxyuridine (**7**, 600 mg, 1.62 mmol) containing 1 mL of sulfuric acid was slowly added a 5 N sodium nitrite solution (0.4 mL). After addition was completed, a solution of sodium azide (0.15 g, 2.3 mmol) in 10 mL of water was added over a period of 30 min with vigorous stirring which resulted in the formation of a reddish-brown precipitate. The reaction mixture was warmed to room temperature and after 2 h the precipitate was collected by filtration and washed with 0.1 N sodium bicarbonate solution and then excess water. Further purification was accomplished by preparative thin layer chromatography on silica gel with methanol (15%) in chloroform as eluent to give compound **9** in 66% yield: mp 155–158 °C; mass spectrum *m/e* 254 (heterocyclic base), 226 (heterocyclic base − N_2), 117; UV (MeOH) λ_{max} 312 nm (ϵ 18 000), 249 (20 000), λ_{min} 275 (15 000); (0.1 N HCl–MeOH) λ_{max} 312 nm (ϵ 18 000), 249 (20 000), λ_{min} 275 (15 000); (0.1 N NaOH–MeOH) λ_{max} 316 nm (ϵ 18 000), λ_{min} 276 (15 000); IR (KBr) 3400, 2120 cm^{-1}; ^1H NMR ($(CD_3)_2CO$) δ 8.25 (s, 1 H, C-6), 7.34 (d, 1 H, J = 16 Hz, PhCH=), 6.79 (d, 1 H, J = 16 Hz, UCH=), 6.20 (t, 1 H, J = 6 Hz, C-1′).

Anal. ($C_{17}H_{17}N_5O_5$, 371.35) C, H, N.

5(*E*)-(3-Nitrostyryl)uridine 5′-Phosphate (12). An aqueous solution (50 mL) containing 1.01 g of uridine 5′-phosphate disodium salt (**10**, 2.72 mmol) and 890 mg of mercuric acetate (2.8 mmol) was heated to 50 °C for 5 h to give **11**. 3-Nitrostyrene (1.6 g, 10.9 mmol) in 10 mL of methanol was added to the warm solution followed by 19.3 mL of 0.141 M lithium tetrachloropalladate (2.72 mmol) in methanol. The mixture was stirred for 30 min, at which time thin layer chromatography on cellulose using 1-butanol–acetone–acetic acid–water–5% ammonium hydroxide (4.5:1.5:1:2:1) indicated that the reaction was complete. The mixture at 25 °C was saturated with hydrogen sulfide gas and filtered through Celite, and the filtrate concentrated in vacuo. Crystals obtained were recrystallized twice from tetrahydrofuran–ethyl ether solution to give 1.05 g (82%) of compound **12**. Further purification on DEAE cellulose using a linear gradient of 0.01–0.40 M triethylammonium bicarbonate buffer, followed by passage through a Dowex-50 (H^+) column, yielded analytically pure compound: mp 162–166 °C dec; mass spectrum *m/e* 259 (heterocyclic base), 242, 229, 212, 188, 171, 142, 115; UV (H_2O) λ_{max} 298 nm (ϵ 17 500), λ_{min} 232 (5500); (0.1 N HCl) λ_{max} 298 nm (ϵ 17 000), λ_{min} 232 (6500); (0.1 N NaOH) λ_{max} 306 nm (ϵ 20 000), λ_{min} 242 (9000); IR (KBr) 1515, 1340 cm^{-1}; ^1H NMR (D_2O, NaOH) δ 8.02 (s, 1 H, C-6), 7.92–7.41 (m, 4 H, aromatic), 7.07 (d, 1 H, J = 16 Hz, PhCH=), 6.82 (d, 1 H, J = 16 Hz, UCH=), 5.90 (d, 1 H, C-1′); (D_2O/NaO_2CCD_3) δ 6.95 (d, 1 H, J = 16 Hz, PhCH=), 6.52 (d. 1 H, J = 16 Hz, UCH=).

Anal. ($C_{17}H_{18}N_3O_{11}P{\cdot}H_2O$, 471.31) C, H; N: calcd, 8.74; found, 8.28.

5(*E*)-(3-Aminostyryl)uridine 5′-Phosphate Hydrochloride (13). Compound **12** (0.5 g, 1.06 mmol) was dissolved in 40 mL of water by adding fused sodium acetate until clear. After dilution with 120 mL of ethanol a solution of hydrazine hydrate (0.1 g, 2 mmol) was added followed by a catalytic amount of Raney nickel (W-2). After the reaction was completed (4 h) the mixture was filtered through Celite and the filtrate concentrated to 15 mL and acidified with 0.5 mL of hydrochloric acid. The precipitate which formed was collected, washed with ethanol and ethyl ether, and dried in vacuo at 40 °C to give 25 mg (6%) of compound **13**: mp 195–210 °C dec; mass spectrum *m/e* 228, 185, 158, 141, 130, 115; UV (0.1 N HCl) λ_{max} 308 nm (ϵ 15 400), λ_{min} 239 (4000); (0.1 N NaOH) λ_{max} 302 nm (ϵ 15 000), λ_{min} 254 (8000); IR (KBr) 3550, 3460, 2580, 2300, 2050 cm^{-1}, no nitro group absorption; ^1H NMR (D_2O, NaOD) δ 7.90 (s, 1 H, C-6), 7.45–6.80 (m, 5 H, aromatic and UCH=), 7.1 (d, 1 H, J = 16 Hz, PhCH=), 6.12 (d, 1 H, C-1′).

Anal. ($C_{17}H_{21}N_3O_9PCl$, 477.79) C, H, N.

5(*E*)-(3-Nitrostyryl)-2′-deoxyuridine 5′-Phosphate (16a). An aqueous solution (40 mL) containing 500 mg of 2′-deoxyuridine 5′-phosphate disodium salt (**14**, 1.42 mmol) and 455 mg of mercuric acetate (1.43 mmol) was heated to 50 °C for 5 h to form the acetoxymercurinucleotide (**15**). Maintaining this temperature, 3-nitrostyrene (750 mg, 9 mmol) in 10 mL of methanol was added with stirring followed by 8.94 mL of 0.14 M lithium tetrachloropalladate. After 30 min the reaction mixture was saturated with hydrogen sulfide gas and filtered through Celite, and the filtrate concentrated in vacuo. Crystals obtained were recrystallized from tetrahydrofuran–ethyl ether solution to yield 430 mg (66%) of compound **16a.** Further purification on DEAE cellulose using a linear gradient of 0.01–0.40 M triethylammonium bicarbonate buffer, followed by passage through a Dowex-50 (H^+) column, yielded analytically pure compound: mp 225–230 °C dec; mass spectrum *m/e* 259, 242, 229, 212, 188, 171, 149, 142, 130, 115; UV (H_2O) λ_{max} 298 nm (ϵ 18 000), λ_{min} 232 (6500); (0.1 N HCl) λ_{max} 298 nm (ϵ 17 000), λ_{min} 232 (7000); (0.1 N NaOH) λ_{max} 306 nm (ϵ 18 000), λ_{min} 242 (8000); IR (KBr) 1515, 1340 cm^{-1}; ^1H NMR (D_2O, NaOD) δ 8.10 (s, 1 H, C-6), 7.90–7.25 (m, 4 H, aromatic), 7.10 (d, 1 H, J = 16 Hz, PhCH=), 6.92 (d, 1 H, J = 16 Hz, UCH=); (D_2O/$NaOOCCD_3$) δ 7.10 (d, 1 H, J = 16 Hz, PhCH=), 6.67 (d, 1 H, J = 16 Hz, UCH=), 6.14 (t, 1 H, C-1′).

Anal. ($C_{17}H_{18}N_3O_{10}P{\cdot}2.5H_2O$, 455.31) C, H, N.

5(*E*)-(4-Nitrostyryl)-2′-deoxyuridine 5′-Phosphate (16b). An aqueous solution (7.5 mL) of 2′-deoxyuridine 5′-phosphate (506 mg, 1.27 mmol) and mercuric acetate (497 mg, 1.50 mmol) was stirred at 50 °C for 5 h. Addition of 4-nitrostyrene (0.65 mL, 3.8 mmol) resulted in the precipitation of the styrene which was partially solubilized by the addition of diethyl ether (20 mL) and methanol (10 mL). After addition of lithium tetrachloropalladate (16 mL, 0.1 M in methanol) the reaction mixture was stirred at 60 °C for 6 h. The workup procedure was identical with that described in the synthesis of **16a** to give 365 mg of **16b** (59%): UV (H_2O) λ_{max} 363 nm (ϵ 21 600), λ_{min} 284 (6600); (0.1 N HCl) λ_{max} 363, λ_{min} 284 nm; (0.1 N NaOH) λ_{max} 378 nm (ϵ 19 500), λ_{min} 294 (7200); mass spectrum *m/e* 259 (heterocyclic base), 188, 115; ^1H NMR (CD_3OD–NaOD) δ 7.88 (2 H, d, J = 9.5 Hz, aromatic), 7.83 (1 H, s, C6-H), 7.45 (2 H, d, J = 9.5 Hz, aromatic), 7.09 (1 H, d, J = 16.5 Hz, PhCH=), 6.66 (1 H, d, J = 16.5 Hz, UCH=) 6.05 (1 H, t, J = 6.3 Hz, C1′-H).

Anal. ($C_{17}H_{18}N_3O_{10}P{\cdot}1.5H_2O$, 455.3) C, H; N: calcd, 8.71; found, 8.28.

5(*E*)-(3-Aminostyryl)-2′-deoxyuridine 5′-Phosphate Hydrochloride (17). An aqueous solution (10 mL) of **16** (46 mg, 0.1 mmol) was treated with 1 drop of hydrazine hydrate and a small amount of Raney nickel (W-2). After the mixture was stirred for 4 h it was quenched by filtration through Celite, 1 drop of hydrochloric acid added, and the solvent partially evaporated. Crystals were obtained that were precipitated from base by the addition of acid and dried in vacuo to yield 20 mg (45%) of compound **17**: mass spectrum *m/e* 228 (heterocyclic base), 168, 157, 143, 130, 113; UV (0.1 N HCl) λ_{max} 308 nm (ϵ 15 000), λ_{min} 239 (4000); (0.1 N NaOH) λ_{max} 302 nm (ϵ 14 500), λ_{min} 254 (9000); ^1H NMR (D_2O, NaOD) δ 8.24 (s, 1 H, C-6), 7.27 (d, 1 H, J = 16 Hz, PhCH=), 6.83 (d, 1 H, J = 16 Hz, UCH=), 6.31 (t, 1 H, C-1′).

Anal. ($C_{17}H_{21}N_3O_9PCl$, 477.79) C, H; N: calcd, 9.10; found, 8.65.

5(*E*)-Styryl-2′-deoxyuridine 5′-Phosphate (18). A solution mixture of the disodium salt of 5-acetoxymercuri-2′-deoxyuridine 5′-monophosphate (**15**, 915 mg, 1.5 mmol) in 10 mL of water prepared as described in the synthesis of **16a**, styrene (468 mg, 4.5 mmol) in 8 mL of tetrahydrofuran, and 16 mL of a 0.1 M methanol solution of lithium tetrachloropalladate (1.6 mmol) was stirred at 50 °C for 5 h. After filtration, saturation with hydrogen sulfide gas, filtration through Celite, and evaporation in vacuo at ambient temperature, the mixture was resolved on a DEAE cellulose column using a linear gradient elution of 600 mL each of 0.01–0.3 M triethylammonium bicarbonate. Fractions 83–118 (830–1180 mL) were combined, lyophilized, and converted to the free acid by passage through a Biorad Ag50-WX8 (H^+) ion exchange resin. After concentration to 10 mL the solution deposited crystals of **18** which were collected by filtration. The filtrate was lyophilized and then dried in vacuo at 35 °C for 24 h to give a combined yield of 316 mg (50%) of compound **18**: mass spectrum *m/e* 214 (heterocyclic base), 171, 144, 117; ^1H NMR (D_2O, CD_3OD) δ 7.8 (s, 1 H, C-6), 7.5–6.9 (m, 6 H, aromatic and vinylic), 6.8 (d, 1 H,

J = 16 Hz, UCH=), 6.13 (t, 1 H, J = 7.2 Hz, C-1′).

Anal. ($C_{17}H_{19}N_2O_8P$, 410.31) C, H, N.

5-(2-Phenylethyl)-2′-deoxyuridine 5′-Phosphate (19). A suspension of 5(*E*)-styryl-2′-deoxyuridine 5′-phosphate (**18**, 200 mg, 0.5 mmol) and 100 mg of 5% palladium on carbon in acetic acid (11 mL) and water (4 mL) was stirred for 2 h under hydrogen gas at 1 atm pressure and room temperature after which time uptake of hydrogen gas had ceased. After filtration through filter paper the filtrate was evaporated and the residue (196 mg) was resolved on a DEAE cellulose column using a linear gradient of 0.01–0.3 M triethylammonium bicarbonate buffer (1000 mL). After lyophilization of fractions 32–53 (15-mL fractions) the residue was converted to the free acid on an Ag50-WX8 (H^+) ion exchange resin and the eluent lyophilized to yield 86 mg (43%) of compound **19**: UV (H_2O) λ_{max} 268 nm (ϵ 9000), λ_{min} 237 (2800); (0.1 N HCl) λ_{max} 268 nm (ϵ 9000), λ_{min} 237 (2800); (0.1 N NaOH) λ_{max} 267 (ϵ 7200), λ_{min} 245 (4900); ^{1}H NMR (D_2O) δ 7.25–6.77 (m, 6 H, C-6 and aromatic), no olefinic protons, 5.93 (t, 1 H, J = 7 Hz, C-1′).

Anal. ($C_{17}H_{21}N_2O_8P \cdot 1.5H_2O$, 412.33) C, H, N.

3-Azidostyrene. An aqueous solution (10 mL) of 3-aminostyrene hydrochloride (1.2 g, 10.07 mmol) containing 1 mL of sulfuric acid was cooled in an ice bath and treated with 13 mL of 1 N sodium nitrite solution. After 1 h an aqueous solution (100 mL) of sodium azide (0.8 g, 12 mmol) was added slowly and then the reaction mixture was warmed to room temperature for 2 h. The reaction mixture was extracted with ethyl ether and the ether layer was washed consecutively with excess 0.1 N sodium bicarbonate solution and water and dried over magnesium sulfate. After filtration and evaporation of ether the crude product was resolved on silica gel with chloroform (20%) in hexane as eluent to give 3-azidostyrene in 75% yield: mass spectrum *m/e* 145 (molecular ion), 117 (M − 28); UV (MeOH) λ_{max} 237 nm (ϵ 24 300), λ_{min} 214 (13 800), sh 300 (900); IR (neat) 2105 cm^{-1} (N_3); ^{1}H NMR (CD_3OD) δ 6.48 (2 dd, PhCH, J_{cis} = 10.5, J_{trans} = 17 Hz), 5.6 (2 d, 1 H, cis PhC=CH, J_{trans} = 17, $J_{geminal}$ = 2 Hz), 5.13 (2 d, 1 H, trans PhC=CH, J_{cis} = 10.5, $J_{geminal}$ = 2 Hz).

5(*E*)-(3-Azidostyryl)-2′-deoxyuridine 5′-Phosphate (20). An aqueous solution (40 mL) of **15** (1.35 mmol) prepared as described in the synthesis of **16a** at 50 °C was treated with 4.6 mL of a 0.274 M solution of lithium tetrachloropalladate (1.42 mmol) in methanol and 3-azidostyrene (350 mg, 2.4 mmol) in 20 mL of methanol. After stirring at 50 °C for 2.5 h the reaction mixture was cooled to 25 °C, saturated with hydrogen sulfide gas, and filtered through Celite, and the filtrate extracted with ethyl ether. After treatment of the aqueous layer with 0.1 N sodium hydroxide solution, the precipitate that formed was filtered and one-half of the filtrate containing product was resolved on a DEAE cellulose column using 1000 mL of a linear gradient of 0.01–0.5 M triethylammonium bicarbonate buffer, the product fractions were lyophilized, and the residue was converted to the free acid by passage through a Dowex-50 (H^+) column to yield after drying 78 mg (25%) of compound **20**: UV (H_2O) λ_{max} 312 nm (ϵ 18 500), 255 (19 000), λ_{min} 275 (15 000); (0.1 N HCl) λ_{max} 312 nm (ϵ 18 500), 255 (20 000), λ_{min} 275 (16 000); (0.1 N NaOH) λ_{max} 308 nm (20 000), 250 (19 000), λ_{min} 275 (15 000); IR (KBr) 2120 cm^{-1} (azide stretching absorption); ^{1}H NMR (D_2O) δ 7.94 (s, 1 H, C-6 H), 7.35 (d, 1 H, J = 17 Hz, PhCH=), 6.87 (d, 1 H, J = 17 Hz, UCH=), 6.45 (t, 1 H, J = 7 Hz, C-1′), 7.3–6.6 (m, aromatic H).

Anal. ($C_{17}H_{18}N_5O_8P \cdot 1.5H_2O$, 451.33) C, H; N: calcd, 14.65; found, 13.86.

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