A Palladium-Catalyzed Coupling Reaction and a Photolytic Reaction for the Direct Synthesis of 5-Arylpyrimidine Nucleotides

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Two reactions were found to be useful for the direct synthesis of 5-arylpyrimidine nucleotides. A palladium-coupling reaction of 5-(chloromercuri)-2'-deoxyuridine (1) with either iodobenzene or 3-nitroiodobenzene afforded low yields of the unsymmetrical biaryl products 5-phenyl-2'-deoxyuridine (3) and 5-(3-nitrophenyl)-2'-deoxyuridine (4). This reaction was used for the synthesis of 5-phenyl-2'-deoxyuridine 5'-phosphate (6) from 2'-deoxyuridine 5'-phosphate in protic solvents without protection of the hydroxyl or phosphate functions. Compound 3 also was prepared in higher yield by photolysis of the trimethylsilyl derivative (8) of 5-iodo-2'-deoxyuridine (7) in benzene. Photolysis of 8 with 2,4-dimethoxybenzene gave 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine (9) in 32% yield. Applications of this reaction to a silyl derivative of 5-iodo-2'-deoxyuridine 5'-phosphate afforded 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine 5-phosphate (14) in 13% yield.

Synthetic methods for the modification of nucleic acids and their monomeric units generally are limited to nucleophilic reactions leading to alkylation of nitrogen or oxygen functions. Bergstrom and co-workers[1] have described a unique reaction that affords pyrimidine nucleosides wherein carbon-5 of the pyrimidine ring couples with olefins to give the modified nucleoside. This reaction has been exploited for the direct modification of nucleotides[2] and polynucleotides;[3] however, the utility of this reaction for the direct synthesis of 5-arylpyrimidine nucleosides or their 5'-phosphate derivatives has not been explore. Such derivatives are desirable as probes to examine the mechanism of the reaction of thymidylate synthetase, a unique enzyme system that catalyzes a two-step alkylation and reduction reaction.[4]

Although synthetic approaches to 5-arylpyrimidines have been described, the literature on the corresponding nucleosides or nucleotides is sparse. Wheeler and Bristol[5] reported the synthesis of 5-phenyluracil and Russell and Hitchings[6] developed a synthetic route to a large series of 5-aryl-2,4-diaminopyrimidines. In both cases the primary route was through condensation of the α-aryl-α-formylacetate ester or acetonitrile with thiourea or guanidine. Taylor and Berger[7] described an elegant route to 5-arylpyrimidines via reductive desulfurization of an intermediate thiophene derivative. 5-Pyridyluracils are found from the thermal reaction of 5-diazouracil with pyridines.[8] None of these methods, however, is practical for the synthesis of the nucleotides or nucleotide derivatives.

Photochemical approaches to 5-arylpyrimidines recently have been reported. Youssefyeh and Lichtenberg[9] obtained 5-phenyl-1,3-dimethyluracil by photolysis of the 5-iodo derivative in benzene. Allen's group reported the preparation of 5-aryl-2,4-dichloropyrimidines also by photolysis of the corresponding 5-iodopyrimidine.[10] Saito and co-workers[11] recently have described that various indoles can be photocoupled to the 5-position of the isopropylidene derivative uridine in an acetone-sensitized photocoupling reaction using the 5-bromo nucleoside.

We sought a procedure for the direct modification of carbon-5 of uracil nucleosides and nucleotides that was regioselective with respect to both the heterocyclic base and the aryl function and would accomodate the diverse functionality and solubility limitations of nucleosides and nucleotides. The subject of this paper is the synthesis of these unsymmetrical biaryl derivatives by two routes: a palladium-catalyzed biaryl coupling reaction and a photochemical coupling reaction. Both of these methods were useful in the conversion of uracil nucleotides to 5-aryluracil nucleotides.

Palladium(0) oxidative coupling of aromatic compounds offers advantages over the usual Ullman coupling reactions leading to biaryl products. The reaction is thought to proceed via the collapse of a bis(aryl)palladium complex.[12] Unfortunately, this method was reported to proceed poorly in polar solvents such as dimethylformamide and acetonitrile, and reduction of catalytic activity in the presence of water limited its potential use with nucleosides or nucleotides. A promising palladium-catalyzed unsymmetrical biaryl synthesis was described which involves the addition of an organomagnesium bromide or organolithium reagent to a phosphine-complexed arylpalladium halide.[13] The resulting diarylpalladium intermediate collapses to the biaryl and regenerates the palladium(0) catalyst. A synthesis of biaryls using organomercury compounds as synthetic intermediates in the presence of copper and a catalytic amount of palladium chloride in pyridine was reported.[14]

None of these methods were ideal for the formation of unsymmetrical biaryl derivatives using pyrmidine nucleosides or nucleotides. The hydroxyl protons and acidic N-3 proton of the pyrimidine ring limit the usefulness of a Grignard reagent. The organomercury compounds gave symmetrical biaryls, and hydroxyl functions inhibited the

(1) (a) Bergstrom, D. E.; Ruth, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 1587-1589. (b) Ruth, J. L.; Bergstrom, D. E. *J. Org. Chem.* **1978**, *43*, 2870-2876. (c) Bergstrom, D. E.; Ogawa, M. K. *J. Am. Chem Soc.* **1978**, *100*, 8106-8112.

(2) (a) Bigge, C. F.; Kalaritis, P. K.; Mertes, M. P. *Tetrahedron Lett.* **1979**, 1653-1656. (b) Bigge, C. F.; Kalaritis, P. K.; Deck, J. R.; Mertes, M. P. *J. Am. Chem. Soc.* **1980**, *102*, 2033-2038.

(3) Bigge, C. F.; Lizotte, K. E.; Panek, J. S.; Mertes, M. P. *J. Carbohydr., Nucleosides, Nucleotides*, in press.

(4) Danenberg, P. V. *Biochim. Biophys. Acta* **1977**, *473*, 73-92.

(5) Wheeler, H. L.; Bristol, H. S. *Am. Chem. Soc. J.* **1905**, *27*, 476-479.

(6) Russell, P. G.; Hitchings, G. H. *J. Am. Chem. Soc.* **1951**, *73*, 3763-3770.

(7) Taylor, E. C.; Berger, J. G. *J. Org. Chem.* **1967**, *32*, 2376-2378.

(8) Keen, B. T.; Paudler, W. W. *J. Org. Chem.* **1975**, *40*, 3717-3720.

(9) Youssefyeh, R. O.; Lichtenberg, L. *J. Chem. Soc.* **1974**, 2649-2654.

(10) Allen, D. W.; Buckland, D. J.; Hutley, B. G.; Oades, A. C.; Turner, J. B. *J. Chem. Soc.* **1977**, 621-624.

(11) Ito, S.; Saito, I.; Matsuura, T. *J. Am. Chem. Soc.* **1980**, *102*, 7535-7541. **Note Added in Proof.** After submission of this manuscript it was noted that 5-phenyluridine was prepared by a photochemical coupling reaction as reported by: Saito, I.; Ito, S.; Shinmura, T.; Matsuura, T. *Tetrahedron Lett.* **1980**, 2813-2816.

(12) Iataaki, H.; Yoshimoto, H. *J. Org. Chem.* **1973**, *38*, 76-79.

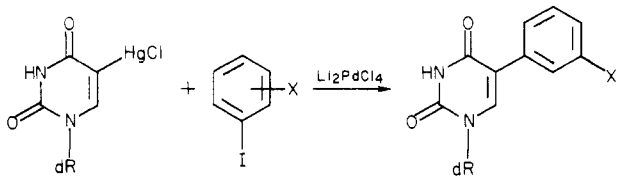
(13) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.* **1976**, *118*, 349-354.

(14) Kretchmer, R. A.; Glowinski, R. *J. Org. Chem.* **1976**, *41*, 2661-2662.

0022-3263/81/1946-1994$01.25/0

reaction.[14] However, it has been found that the 5-chloromercuri derivative of 2'-deoxyuridine 5'-phosphate can be transmetalated to give the corresponding aryl-palladium(II) complex, a useful intermediate in the synthesis of 5-styryl-substituted deoxyuridine nucleotides.[2b]

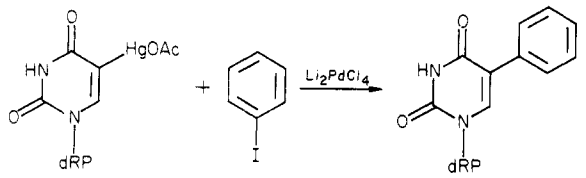
The nucleosides 5-phenyl-2'-deoxyuridine (**3**) and 5-(3-nitrophenyl)-2'-deoxyuridine (**4**) were prepared by stirring 1 equiv of lithium tetrachloropalladate with 5-(chloromercuri)-2'-deoxyuridine (**1**) for 1 h. Addition of iodobenzene (**2a**) or 1-iodo-3-nitrobenzene (**2b**) in solution to the reaction mixture followed by stirring at room temperature for 72 h gave the products **3** and **4** in 10% yield. Preparation of 5-(4-nitrophenyl)-2'-deoxyuridine was not achieved under identical conditions, or with acetic acid and ethanol as the reaction solvent to improve solubility of 1-iodo-4-nitrobenzene. Higher reaction temperatures did not facilitate the reaction since stirring at reflux gave only a 2.3% yield of 5-phenyl-2'-deoxyuridine (**3**) and also yielded 5-phenyluracil as a byproduct. The order of addition of reagents was not important since stirring the aryl iodide (**2b**) with lithium tetrachloropalladate prior to the addition of the mercuri derivative again gave a 10% yield of **4**.



1 **2a**, X = H; **b**, X = *m*-NO_2 **3**, X = H; **4**, X = *m*-NO_2

Various reaction conditions were used to determine the requirements of the reaction. Reactions in which 2'-deoxyuridine was used instead of the mercuri derivative **1** failed to give adduct formation, which indicates that it is essential to activate the nucleoside moiety at carbon-5. The use of catalytic amounts of palladium(II) gave lower yields than equivalent amounts.

More importantly, this unsymmetrical biaryl synthetic method was extended to the direct coupling of iodobenzene to a nucleotide. 5-Phenyl-2'-deoxyuridine 5'-phosphate (**6**) was prepared in 4.3% yield by treating an aqueous solution of 5-(acetoxymercuri)-2'-deoxyuridine 5'-phosphate (**5**) and iodobenzene (**2a**) (solubilized with tetrahydrofuran) with lithium tetrachloropalladate in methanol and refluxing for 15 h.

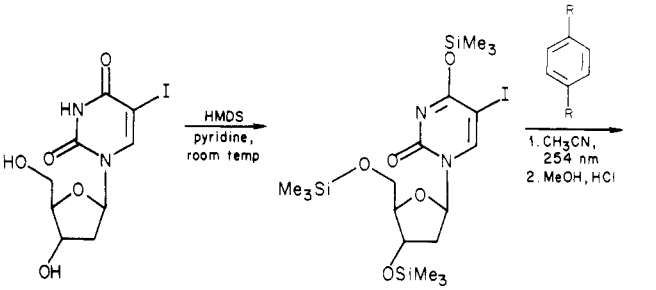


5 **2a** **6**

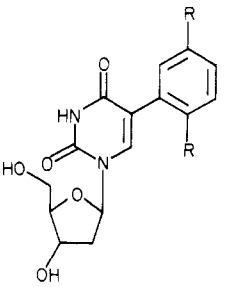
The mechanism for this reaction which most probably proceeds via a zero-valent palladium complex is currently being studied as are conditions for improving the yields.

Photolysis of 5-iodopyrimidines in benzene or heteroarenes gave high yield of the C-5 adducts.[10] In the only previous reports involving a uracil base, it was shown that photolysis of 5-iodo-1,3-dimethyluracil in benzene gives a 54% yield of the 5-phenyl derivative[9] and a protected 5-bromouridine derivative photocoupled with indole derivatives.[11]

The trimethylsilyl derivative (**8**) of 5-iodo-2'-deoxyuridine (**7**) was prepared with hexamethyldisilazane in pyridine at room temperature; the product was used without further purification after removal of pyridine in vacuo. The nucleosides 5-phenyl-2'-deoxyuridine (**3**) and 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine (**9**) were prepared in 18% and 32% yield, respectively, by irradiating solutions of **8** in deoxygenated benzene, or 1,4-dimethoxybenzene in acetonitrile, at 254 nm in a quartz reaction vessel. Yields were dependent on the time of irradiation; short reaction time (<2 h) gave the recovery of unreacted iodonucleoside **8**, while long reaction time gave a more complex mixture of products.



7 **8**



3, R = H
9, R = OCH_3

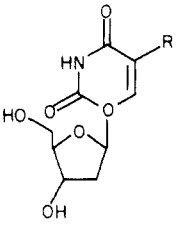
The critical reaction was to apply the photochemical coupling procedure to nucleotides. Again, solubility was the major problem. Attempts to prepare the trimethylsilyl derivative of 5-iodo-2'-deoxyuridine 5'-monophosphate (**10**) were unsuccessful because of either rapid hydrolysis or the adduct did not form.

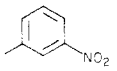
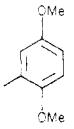
An acid-catalyzed silylating reagent, 4-[(*tert*-butyldimethylsilyl)oxy]-3-penten-2-one (**12**),[15] was stirred with 5-iodo-2'-deoxyuridine 5'-phosphate (**10**) in dimethylformamide at room temperature for 44 h. The reagent produces 2,4-pentadione and is believed to proceed through the highly reactive *tert*-butyldimethylsilenium cation. After removal of the dimethylformamide in vacuo the uncharacterized silyl derivative (**13**) was used without purification in the photochemical coupling reaction with 1,4-dimethoxybenzene in acetonitrile. The product, 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine 5'-phosphate (**14**; Scheme I) was obtained in 13% yield and identified by its ultraviolet and mass spectrum, giving the heterocyclic fragment 5-(2,5-dimethoxyphenyl)uracil, arising from cleavage of the glycoside bond. The structure of **14** was confirmed by phosphorylation of the respective nucleoside **9** according to the procedure of Sowa and Ouchi[16] to give compound **14** with a mass spectrum identical with that obtained from the direct coupling reaction.

The introduction of a phenyl group into the 5-position of pyrimidines is reported to promote a shift in the ultraviolet absorption maxima to longer wavelengths because of the planar biaryl orientation which allows for greater electron delocalization.[17] In the 5-aryl-2,4-diamino-

(15) Veysoglu, T.; Mitscher, L. A. *Tetrahedron Lett.* **1981**, 1299–1302.
(16) Sowa, T.; Ouchi, S. *Bull Chem. Soc. Jpn.* **1975**, *48*, 2084–2090.

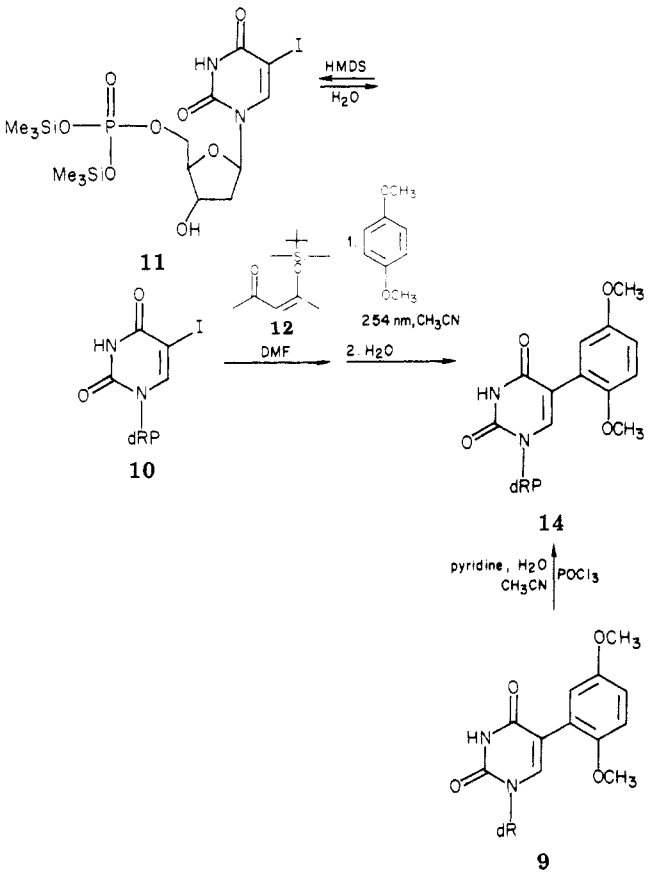
Table I. Ultraviolet Spectral Data of 5-Aryl-2'-deoxyuridines



compd	R	λ, nm (ε) 0.1 N HCl	H_2O	0.1 N NaOH
3		279 (10 700), 258 (7900)	279 (9300), 258 (6600)	268 (8300), 261 (8200)
4		277 (16 000), 258 (12 800)	277 (15 400), 258 (12 300)	273 (14 800), 266 (14 800)
9		265 (9750), 245 (8200)	265 (10 250), 245 (8200)	270 (7400)[a]

[a] The solvent in this case was 0.3 N NaOH and the 270-nm peak was a shoulder.

Scheme I



pyrimidine series substitution either at the 6 position of the pyrimidine ring or the ortho position on the aryl ring prevented the coplanar orientation and gave an ultraviolet spectrum that resembled the parent pyrimidine ring.[6] Acidic solutions of 5-substituted uracil nucleosides with an sp^3 carbon joined at this position normally have an ultraviolet maxima at 270 nm or below. A red shift is noted where an sp^2 or sp carbon is substituted at carbon-5 of 2'-deoxyuridine 5'-phosphate (formyl, 278 nm; cyano, 276 nm; 3-nitrostyryl,[2b] 298 nm; styryl,[2b] 305 nm; 4-nitrostyryl,[2b] 363 nm). Both 5-phenyl (3) and 5-(3-nitrophenyl)-2'-deoxyuridine (4) have extended conjugation with ultraviolet maxima at 279 and 277 nm, respectively. The 5-dimethoxyphenyl derivative 9 is not thought to be coplanar since the ultraviolet maxima is 265 nm; in this case steric hindrance by the ortho methoxy group prevents the extended resonance interaction (Table I).

The results of these studies demonstrate that the palladium biaryl coupling procedure is regioselective with respect to both the nucleoside or nucleotide and the aryl iodide and can be used with the unprotected molecules. The yields are low; however, they have not been optimized. The higher yielding photochemical coupling reaction requires that the nucleosides and nucleotides be derivatized prior to reaction to increase solubility in nonpolar solvents. The silylating reagent, 4-[(*tert*-butyldimethylsilyl)oxy]-3-penten-2-one[15] was useful for the derivatization of nucleotides.

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 recording spectrophotometer, ^{1}H-NMR spectra with a Varain Model EM-360 or T-60 or a Perkin-Elmer R-32. Microanalyses were obtained from a Hewlett-Packard 185B and mass spectra from a Varian CH5 spectrometer. Unless indicated C, H, N analyses were ±0.4% of the calculated values. DEAE cellulose was a product of Whatman Biochemical Ltd.; 2'-deoxyuridine (B-grade) and 2'-deoxyuridine 5'-phosphate were purchased from Calbiochem or Sigma; 5-iodo-2'-deoxyuridine and 5-iodo-2'-deoxyuridine 5'-phosphate were purchased from Vega and Calbiochem, respectively.

A Rayonet Model RPR 100 photochemical reactor and the corresponding 254-nm lamps are products of Southern N.E. Ultraviolet Co. A motorized rotating stand kept 15-mL quartz reaction tubes a constant distance (~2 cm) from the light source. High-performance LC was performed with a Waters Model M6000A and a Perkin Elmer LC-15 UV detector with Partisil PXS 10/25 SAX (strong anion exchange) or Partisil PXS 10/25 ODS-II columns.

5-Phenyl-2'-deoxyuridine (3). Method A. A suspension of 5'-(chloromercuri)-2'-deoxyuridine (1, 370 mg, 0.8 mmol) and lithium tetrachloropalladate (0.85 mmol) in 34 mL of methanol

(17) Maggiolo, A.; Russell, P. B. *J. Chem. Soc.* **1951**, 3297–3300.

was stirred at room temperature for 1 h. After addition of iodobenzene (**2a**, 0.9 mL, 0.8 mmol), the reaction mixture was stirred at room temperature for 72 h, quenched by saturating with hydrogen sulfide gas, and filtered through Celite, and the filtrate evaporated. Resolution of the mixture on Florisil was accomplished by eluting with 0–20% methanol in ethyl acetate to give 24 mg (0.08 mmol, 10%) of **3** after recrystallization from ethanol: mp 193–194.5 °C; mass spectrum, *m/e* 304 (1.1, molecular ion), 188 (100, 5-phenyluracil), 145 (15), 144 (26), 117 (32), 2'-deoxyribose); IR (KBr) 3440 (b), 1690, 775, 740, 685 cm^{-1}; ^1H NMR (CD_3OD) δ 8.26 (s, 1 H, C6-H), 7.68-7.27 (m, 5 H, aromatic), 6.36 (t, 1 H, J = 6 Hz, C_1'-H).

Anal. ($C_{15}H_{16}N_2O_5$, M_r 304.30) C, H, N.

Conditions identical with those in method A except the reaction was stirred at reflux for 24 h gave 5-phenyl-2'-deoxyuridine (**3**) in 2.3% yield. In addition, 5-phenyluracil (2.7%) was isolated: mass spectrum, *m/e* 188 (100, molecular ion), 145 (46, molecular ion – HNCO), 104 (70, molecular ion – 2 NCO), 77 (26, phenyl); ^1H NMR (CD_3OD) δ 7.8–7.49 (m, 5 H, aromatic), 5.87 (s, 1 H, C-6).

Method B. A solution of 5-iodo-2'-deoxyuridine (**7**, 500 mg, 1.41 mmol) and hexamethyldisilazane (323 mg, 2 mmol) in 5 mL of anhydrous pyridine was stirred under an argon atmosphere overnight at room temperature. After removal of the pyridine in vacuo, the residue was dissolved in 20 mL of freshly distilled benzene, deoxygenated with argon, and irradiated in a quartz reaction vessel with ten 254-nm lamps in a Rayonet photochemical reactor for 48 h. The silyl protecting groups were removed by stirring the solution with 20 mL of 0.1 N HCl in methanol which precipitated unreacted 5-iodo-2'-deoxyuridine. Resolution of the reaction mixture on silica with 0–20% methanol in chloroform gave 78 mg (0.26 mmol, 18.4%) of compound **3**.

5-(3-Nitrophenyl)-2'-deoxyuridine (4). A solution of 1-iodo-3-nitrobenzene (**2b**, 500 mg, 2 mmol) and lithium tetrachloropalladate (2 mmol) in 40 mL of methanol was stirred for 1 h at room temperature. After 5-(chloromercuri)-2'-deoxyuridine (1, 926 mg, 2 mmol) was added, the reaction mixture was refluxed for 72 h, cooled to room temperature, saturated with hydrogen sulfide, and filtered through Celite. The residue was evaporated and chromatographed on Florisil with 0–50% methanol in ethyl acetate as eluent; resolution on silica with 0–10% methanol in ethyl acetate gave 70 mg (0.18 mmol, 10%) of compound **4** after recrystallization from methanol: mp 201.5–202.5 °C; mass spectrum, *m/e* 349 (0.5, molecular ion), 233 (100, 5-(3-nitrophenyl)uracil), 189 (61), 143 (13), 117 (43, 2'-deoxyribose); IR (KBr) 3430, 1710, 1695, 1655, 1520, 1460, 1350 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 8.7–7.65 (m, 5 H, aromatic, C6-H), 6.31 (t, 1 H, J = 6.3 Hz, C_1'-H).

Anal. ($C_{15}H_{15}N_3O_7$, M_r 349.29) C, H, N.

5-Phenyl-2'-deoxyuridine 5'-Phosphate (6). A solution of 5-(acetoxymercuri)-2'-deoxyuridine 5'-phosphate (**5**, 0.6 mmol) in 3 mL of water containing mercuric acetate (sixfold excess) was treated with a solution of iodobenzene (**2a**, 0.1 mL) in 1 mL of tetrahydrofuran and then with lithium tetrachloropalladate (7 mL of a 0.1 M solution in methanol). After being stirred for 15 h at reflux, the reaction mixture was cooled, saturated with hydrogen sulfide gas, and filtered through Celite, and the filtrate was resolved on DEAE cellulose, using 700 mL of 0.01 to 0.3 M triethylammonium bicarbonate buffer (pH 7.5) in a linear gradient followed by 500 mL of 0.3 to 0.5 M buffer. Fractions 69–76 (10 mL each) were combined and lyophilized to give 15 mg (4.3%) of **6** as a hygroscopic, white powder: mass spectrum, *m/e* 188 (21, 5-phenyluracil), 145 (8), 117 (3), 101 (100, triethylamine), 77 (7); analysis by high-performance LC on Partisil PXS 10/25-SAX with 0.04 M KH_2PO_4 buffer, 2 mL/min, gave a single peak with a retention time of 2.2 min. Passage through a Biorad AG50 WX-8 (H^+) column converted the material to its free acid (UV (H_2O) λ_{max} 278, λ_{min} 255 nm).

5-(2,5-Dimethoxyphenyl)-2'-deoxyuridine (9). A solution of 5-iodo-2'-deoxyuridine (**7**, 1.307 g, 3.69 mmol) and hexamethyldisilizane (650 mg, 4.03 mmol) in 10 mL of anhydrous pyridine was stirred at room temperature overnight; the solvent was then evaporated in vacuo at ambient temperature. A solution of the residue and 1,4-dimethoxybenzene (3.06 g, 22.14 mmol) in 20 mL of anhydrous acetonitrile was distributed into four 15-mL quartz tubes, deoxygenated with argon gas, and irradiated for 24 h with 13 254-nm lamps in a Rayonet photochemical reactor equipped with a rotating tube carrier. After the acetonitrile was evaporated, the silyl protecting groups were removed with hydrochloric acid in methanol (~10%), the solution was evaporated, and the mixture was resolved on a silica column with 10% methanol in chloroform as eluent to yield 428 mg of **9** (1.18 mmol, 32%) as a tan powder (attempts to crystallize this material failed): mp 125–130 °C; mass spectrum, *m/e* 364 (16, molecular ion), 248 (100, 5-(2,5-dimethyoxyphenyl)uracil), 233 (28), 219 (9), 217 (10), 205 (10), 190 (20), 174 (14), 162 (44), 117 (9); IR (KBr) 3450, 1675, 1500, 1460, 1415, 855, 790 cm^{-1}; ^1H NMR (CD_3OD) δ 7.8 (s, 1 H, C6-H), 6.7 (s, 3 H, aromatic), 6.17 (t, 1 H, C_1'-H), 3.63 (s, 6 H, OCH_3).

Anal. ($C_{17}H_{20}N_2O_7 \cdot H_2O$, M_r 382.37) C, H, N.

5-(2,5-Dimethoxyphenyl)-2'-deoxyuridine 5'-Phosphate (14). Method A. An aqueous solution of 5-iodo-2'-deoxyuridine 5'-phosphate diammonium salt monohydrate (**10**, 100 mg, 0.21 mmol) was passed through an AG50-WX8 (H^+) ion-exchange column to generate the free acid and lyophilized. The freeze-dried product was dissolved in 2 mL of freshly distilled anhydrous dimethylformamide under argon and treated with [(*tert*-butyldimethyl-4-silyl)oxy]-3-penten-2-one[15] (190 μL) for 44 h at room temperature. After removal of the solvent and excess reagent in vacuo, the vacuum was released to an argon atmosphere and the residue containing **13** was dissolved in 2 mL of anhydrous acetonitrile in a quartz reaction tube. A solution of 1,4-dimethoxybenzene (175 mg, 1.26 mmol) in 2 mL of anhydrous acetonitrile was added, and the mixture was deoxygenated with argon and irradiated with 13 254-nm lamps for 20 h. After being shaken with 3 mL of water, the reaction mixture was extracted with diethyl ether (2 × 10 mL) and the ether layer back-extracted with 5 mL of 5% sodium carbonate. The aqueous layers were combined, neutralized with acetic acid, diluted to 15 mL with water, and resolved on DEAE cellulose with a linear gradient of triethylammonium bicarbonate (300 mL each of 0.01 to 0.3 M, pH 7.5). High-performance LC analysis of fractions 40–44 (Partisil PSX 10/25-SAX, 0.03 M KH_2PO_4, pH 3.75, 2 mL/min) coinjected with dUMP; fractions 45–51, which contained dUMP as an impurity by high-performance LC, were combined, lyophilized, and rechromatographed on DEAE cellulose to give **14** as a single symmetrical peak in 13% yield: mass spectrum, *m/e* 248 (100, 5-(2,5-dimethoxyphenyl)uracil), 233 (22), 219 (7), 217 (6), 205 (11), 190 (24), 174 (27), 162 (94); UV (H_2O) λ_{max} 265 nm, λ_{min} 245.

Method B.[16] A solution of freshly distilled phosphorus oxychloride (2.01 mL) in 5 mL of anhydrous acetonitrile at 0 °C was treated dropwise and very slowly with 0.22 mL of distilled water and stirred at 0 °C for 1 h. Pyridine (1.9 mL) was added dropwise even more slowly to the cold solution; the mixture was diluted to 10 mL with anhydrous acetonitrile, and 0.45 mL of this solution was added at 0 °C to 5-(2,5-dimethoxyphenyl)-2'-deoxyuridine (**9**, 100 mg, 0.27 mmol). After the reaction mixture was stirred at 0 °C for 5 h, it was quenched with 0.5 mL of water, neutralized by adding triethylamine slowly, diluted to 5 mL, and resolved on DEAE cellulose with a linear gradient of triethylammonium bicarbonate buffer, pH 7.5 (1000 mL, 0.01 to 0.3 M). The triethylammonium salt was neutralized with acetic acid and passed through an AG50-WX8 (H^+) ion-exchange column to give 40 mg (0.09 mmol, 33%) of compound **14**: the mass spectrum has the same fragmentation pattern as that from method A; UV (H^+) λ_{max} 265 nm, λ_{min} 245.

Anal. ($C_{17}H_{21}N_2O_{10}P \cdot CH_3CO_2H \cdot H_2O$, M_r 522.403) C, N; H, calcd 5.21, found 4.80.

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