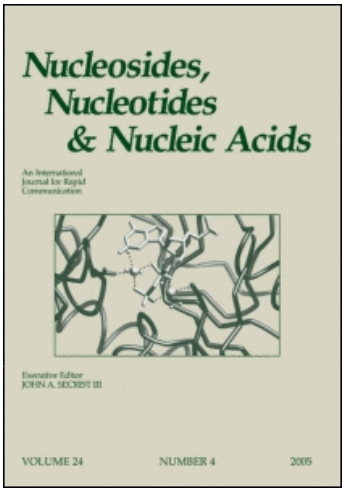

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

A New Approach for the Synthesis of Novel 5-Substituted Isodeoxyuridine Analogs

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Online publication date: 02 October 2004

To cite this Article Guenther, Sven and Nair, Vasu(2004) 'A New Approach for the Synthesis of Novel 5-Substituted Isodeoxyuridine Analogs ', Nucleosides, Nucleotides and Nucleic Acids, 23: 1, 183 — 193
To link to this Article: DOI: 10.1081/NCN-120027827
URL: http://dx.doi.org/10.1081/NCN-120027827

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 23, Nos. 1 & 2, pp. 183–193, 2004

A New Approach for the Synthesis of Novel 5-Substituted Isodeoxyuridine Analogs[†]

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ABSTRACT

Cyclic sulfates of carbohydrates provide excellent synthons for the preparation of isodeoxyuridines through direct nucleophilic substitution reactions. These substitution reactions have exceptional regioselectivity. The products of the reactions served as key precursors for the synthesis of 5-substituted isodeoxyuridines via the Stille and Heck coupling reactions. Interestingly, unprotected nucleosides could be used in these metal-mediated functionalizations. The methodologies are general and allow ready access to a variety of C-5 functionalized isomeric deoxyuridines, but also have the potential to be extended to other nucleoside analogs.

Key Words: Synthesis; Functionalized isouridines; Cyclic sulfate; Cross-coupling reactions.

[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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DOI: 10.1081/NCN-120027827 1525-7770 (Print); 1532-2335 (Online)

INTRODUCTION

The quest for improved antiherpetic drugs gave rise to the development of a variety of new antiviral agents.[1] Many nucleoside analogs, including certain 5-substituted 2′-deoxyuridine derivatives were found to exhibit potent activity against the herpes simplex virus (HSV).[2,3] Among these compounds, one of the most active analogs against HSV-1 is (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU, Figure 1).[4] However, 5-substituted 2′-deoxyuridines including BVDU are rapidly degraded in vivo by cellular pyrimidine nucleoside phosphorylases (thymidine phosphorylase and/or uridine phosphorylase).[5,6] In order to increase their intracellular stability we designed new isomeric analogs of BVDU, in which the pyrimidine base is attached to the C-2′ position instead of the natural C-1′ position of the carbohydrate moiety. In previous work with isomeric dideoxynucleosides,[7–9] we have shown that this type of alteration of the glycosyl bond results in complete resistance toward nucleoside phosphorylases.[10] As the target enzyme of herpes virus inhibitors (in their triphosphate form) is the HSV-1 DNA polymerase, it is imperative that these compounds be phosphorylated by viral or host kinases. Preliminary molecular modeling studies showed that some 5-substituted isomeric 2′,3′-dideoxyuridine and 2′-deoxyuridine derivatives are likely substrates for HSV-1 thymidine kinase (TK).[11] This enzyme plays an important role in the initial and crucial conversion to the nucleoside monophosphates, which are subsequently phosphorylated by less specific cellular monophosphate and disphosphate kinases.[12]

Recently, we have reported on the synthesis and biological evaluation of (*E*)-5-(2-bromovinyl)isodideoxyuridine (BVisoDDU, Figure 1). Interestingly, this compound is phosphorylated by HSV-1 TK and showed potent activity against three different strains of HSV-1.[11] The parent isonucleoside was completely resistant to cleavage by thymidine phosphorylase. However, the approach used by us in the synthesis of BVisoDDU[11] was cumbersome and required improvement. In addition, the synthesis involved construction of the uracil ring system from a β-amino precursor which introduced several additional steps in the synthesis. The present study describes a general approach to the synthesis of 5-substituted isodeoxyuridines.

RESULTS AND DISCUSSION

The key carbohydrate precursor was the cyclic sulfate, **2** (Scheme 1), prepared from readily available **1** by conversion to the cyclic sulfite and subsequent oxidation

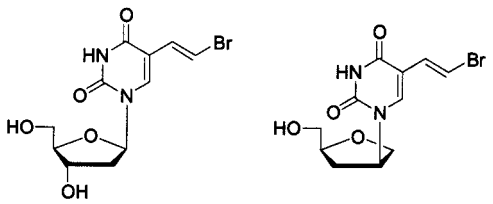

Figure 1. Comparison of the structures of BVDU and BVisoDDU.

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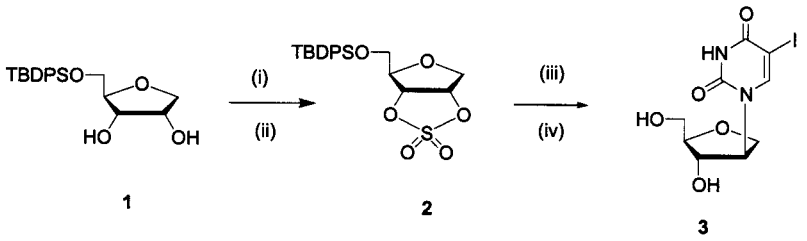
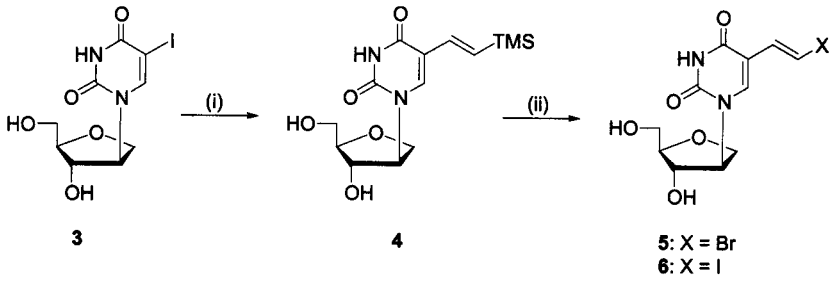


(i) $SOCl_2$, Py (ii) $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O (iii) 5-I-Ura, DBU, CH_3CN (iv) HCl_{aq}, MeOH

Scheme 1. Condensation of cyclic sulfate **2** with 5-iodouracil and subsequent conversion to unprotected precursor **3**.

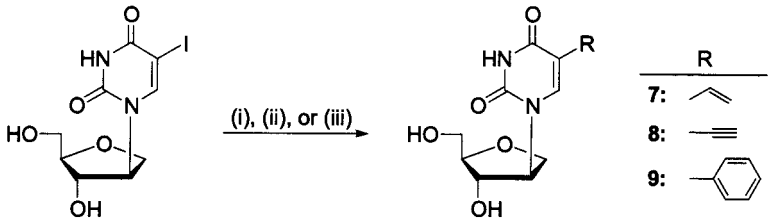
with $RuCl_3/NaIO_4$ under phase-transfer catalysis.[13,14] Direct coupling of the cyclic sulfate **2** with 5-iodouracil and DBU in refluxing CH_3CN resulted in regioselective attack at position 2 to give a ring-opened sulfate that was immediately hydrolyzed with aqueous methanolic HCl to give the isodeoxynucleoside **3** in 51% overall yield (2 steps). The high regioselectivity of the coupling reaction can be explained by the presence and proximity of the bulky *tert*-butyldiphenylsilyl group that hindered ring opening at C-3 and thus the formation of a second regioisomer.

The various 5-substituents were then introduced via Heck or Stille reactions of **3** with palladium (II) catalysts and organostannanes as cross-coupling reagents.[15–19] Interestingly, unprotected nucleosides can be used in all of these cross-coupling reactions. As shown in Scheme 2, BVisoDU (**5**) and IVisoDU (**6**) were synthesized in two steps from **3** by conversion to **4** (65% yield) using trimethyl(2-tributylstannanylvinyl)silane[20] and $(Ph_3P)_2Pd(II)Cl_2$ and subsequent replacement of the trimethylsilyl group of **4** with a halogen by treatment with LiBr or NaI and XeF_2.[21] The yields in the last steps (halogen exchange of TMS group) were relatively low, possibly due to the poor solubility of the polar nucleoside analogs in benzene. This solvent was chosen because it had been reported to yield very high *E/Z* ratios with respect to the stereochemistry of the vinylic double bonds of the resulting products.[21] Indeed, we found that the *E*-isomer was formed almost exclusively under these conditions as confirmed by ^1H NMR spectral data ($^2J_{vinyl}$ = 13.6 Hz for the two *trans*-vinylic protons).



(i) *n*-$Bu_3SnCH{=}CHTMS$, $(Ph_3P)_2Pd(II)Cl_2$, CH_3CN (ii) LiBr (NaI), XeF_2, benzene

Scheme 2. Synthetic route for the preparation of BVisoDU and IVisoDU from **3**.



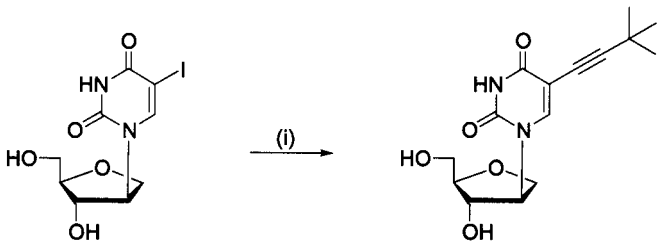
3

(i) n-$Bu_3SnCHCH_2$, $(Ph_3P)_2Pd(II)Cl_2$, CH_3CN (ii) n-Bu_3SnCCH, $(Ph_3P)_2Pd(II)Cl_2$, CH_3CN (iii) n-Bu_3SnPh, $(Ph_3P)_2Pd(II)Cl_2$, CH_3CN

Scheme 3. Introduction of unsaturated 5-substituents via Stille cross-coupling reaction.

Applying Stille cross-coupling conditions, compounds **7**, **8**, and **9** were prepared directly from precursor **3** in excellent to moderate yields, respectively (Scheme 3).

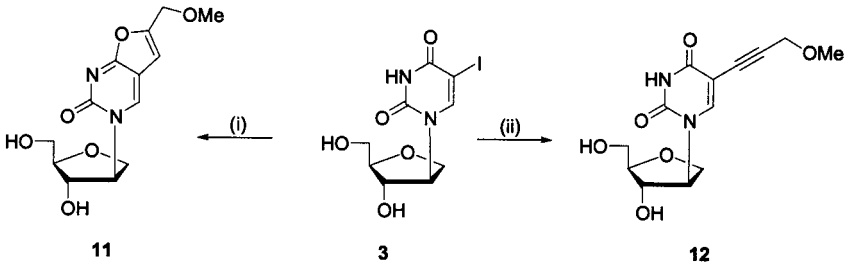
Introduction of substituted alkynes was also of interest in this synthetic work. The Heck reaction with **3** and 3,3-dimethyl-but-1-yne in Et_3N and THF using $(Ph_3P)_2Pd(II)Cl_2$ and CuI as catalysts gave compound **10** (Scheme 4). Although the reaction time for this conversion was moderately long (18 h), the reaction proceeded very smoothly in THF at room temperature to give **10** in 91% yield. The analogous reaction with 3-methoxypropyne as coupling agent in THF was more sluggish at room temperature and consequently it was necessary to increase the temperature to 70°C. This, however, induced cyclization of the side-chain resulting in the formation of the furanopyrimidone compound **11** as the major product (Scheme 5). This type of fluorescent bicyclic nucleoside derivatives as side-products of other cross-coupling reactions with alkynyl reagents has been reported.[17,22] However, changing the solvent from THF to DMF completely circumvented formation of the furanopyrimidone and allowed the reaction to proceed at room temperature with faster reaction rates and with good yields of the desired product **12**. The ^1H and ^{13}C NMR data for all final compounds are presented in Table 1 for ease of comparison.



3 10

(i) $HCCCMe_3$, $(Ph_3P)_2Pd(II)Cl_2$, CuI, Et_3N, THF

Scheme 4. Synthesis of **10** via the Heck reaction.



11 3 12

(i) $HCCCH_2OMe$, $(Ph_3P)_2Pd(II)Cl_2$, CuI, Et_3N, THF, 70°C, 2 d (ii) $HCCCH_2OMe$, $(Ph_3P)_2Pd(II)Cl_2$, CuI, Et_3N, DMF, 25°C, 2 h

Scheme 5. Synthesis of **12** and formation of bicyclic furanopyrimidone derivative **11** via the Heck reaction.

In summary, methodologies for the synthesis of isodeoxyuridines through the direct nucleophilic substitution reaction of 5-iodouracil anion with a carbohydrate cyclic sulfate is described. The substitution reaction has high regioselectivity. The product of this reaction served as the key precursor for the synthesis of 5-substituted isodeoxyuridines via the Stille and Heck coupling reactions. It is significant to note that these cross-coupling reactions could be carried out with totally unprotected nucleosides. The methodologies described are general.

EXPERIMENTAL

The melting points are uncorrected and were determined with an Electrothermal Engineering Ltd. melting point apparatus. UV spectra were obtained using a Varian Cary 3 UV–visible spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-400 (400 MHz and 100 MHz, respectively) and Varian Mercury Plus 400 (400 MHz and 100 MHz, respectively) instruments. Chemical shifts are referenced to solvent peaks (acetone–d_6, $CDCl_3$, DMSO–d_6, or MeOH–d_4) orto TMS as internal standard. NMR signals were assigned by matching the spectra with literature data and by comparing ambiguous signals with signal changes from NMR data of previous steps or closely related compounds. Silica gel, 230–400 mesh, was employed for column chromatographic separations. High-resolution FAB mass spectral data were acquired on a Kratos MS-50 high resolution mass spectrometer or a Micromass Autospec high resolution mass spectrometer. HPLC experiments were carried out on a Beckman Coulter System Gold (125P Solvent Module and 166P Detector) using either a 300 mm × 30 mm or a 300 mm × 19 mm Deltapak C-18, 15 μm, 100 Å column (unless specified otherwise). Anhydrous solvents were obtained from Aldrich® or Acros™ in sealed containers under nitrogen or argon. All other reagents and solvents were used directly as they were obtained from the manufacturer without further purification.

1-(4-Hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-5-iodo-1*H*,3*H*-pyrimidine-2,4-dione (3). To a solution of 52.3 g (220 mmol) of 5-iodouracil in 500 mL of dry CH_3CN was added 31.0 mL (220 mmol) of DBU. The reaction mixture was heated

Table 1. 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectral data of the final 5-substituted 2′-deoxyuridine analogs.

Nucleus	Compound							
	3[a]	5[b]	6[b]	7[b]	8[b]	9[b]	10[b]	12[b]
				^{1}H shifts for sugar moiety				
H-1′	3.97 dd	4.16 dd	4.14 dd	4.16 dd	4.15 dd	4.19 dd	4.14 dd	4.15 dd
	3.91 dd	4.05 dd	4.04 dd	4.04 dd	4.04 dd	4.10 dd	4.02 dd	4.05 dd
H-2′	4.75 m	4.94 m	4.93 m	4.95 m	4.91 m	5.01 m	4.91 m	4.91 m
H-3′	4.17 m	4.29 dd	4.28 dd	4.32 dd	4.27 dd	4.38 dd	4.26 dd	4.27 m
H-4′	3.65 m	3.88 dt	3.86 dt	3.86 dt	3.83 dt	3.86 m	3.84 dt	3.84 dt
H-5′	3.55 m	3.67 m	3.69 m	3.71 m	3.69 m	3.72 m	3.70 m	3.70 m
				^{1}H shifts for base moiety				
H-6	8.12 s	7.86 s	7.85 s	7.86 br d	8.09	7.94 s	7.89 s	8.06 s
				^{13}C shifts for sugar moiety				
C-1′	69.35/ 69.02	71.25	71.12	71.29	71.04	70.74	70.85	70.91
C-2′	63.44	65.74	65.59	65.61	66.06	65.36	65.62	65.88
C-3′	75.35	77.89	77.40	77.77	77.76	77.39	77.42	77.63
C-4′	85.83	87.72	87.57	87.53	87.61	86.75	87.21	87.48
C-5′	60.20	61.74	61.57	61.78	61.85	61.30	61.70	61.70
				^{13}C shifts for base moiety				
C-2	150.70	152.00	151.84	152.29	152.03	152.58	151.94	151.85
C-4	160.53	163.78	163.69	164.47	164.54	164.85	164.47	164.29
C-5	69.35/69.02	112.46	113.95	115.66/113.77	99.98	116.80	101.47	100.02
C-6	146.80	130.48	137.73	129.40	147.96	141.41	145.54	147.29

[a]In DMSO–d_6.
[b]In MeOH–d_4.

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under reflux for 1 h and then cooled to 25°C. To the 5-iodouracilate solution was then added a solution of 91.0 g (209 mmol) of **2**[13,14] in 500 mL of dry CH_3CN. The mixture was heated under reflux for another 1.5 h. The solvent was evaporated and the residue was purified by column chromatography (60:3:1 CH_2Cl_2/MeOH/Et_3N) to give the protected substitution product which was used directly for the subsequent deprotection reaction in 750 mL of MeOH and 20 mL of conc. HCl. This mixture was heated for 19 h to 50°C, cooled down to room temperature and the pH adjusted to 4 with aqueous NaOH. The solvents were then evaporated and the resulting residue was purified by column chromatography (0–100% EtOAc/hexanes) to yield 38.0 g (51% overall yield for 2 steps) of **3**: mp 215°C (decomp.). UV (MeOH) λ_{max} 273, 216 nm. ^{1}H NMR (DMSO–d_6): δ 11.67 (br s, 1H, 3-NH), 8.12 (s, 1H, H-6), 5.63 (d, 1H, J = 5.2 Hz, 3′-OH), 4.97 (t, 1H, J = 5.2 Hz, 5′-OH), 4.75 (m, 1H, H-2′), 4.17 (m, 1H, H-3′), 3.97 (dd, 1H, J = 6.8, 10.4 Hz, H_a-1′), 3.91 (dd, 1H, J = 4.4, 10.4 Hz, H_b-1′), 3.65 (m, 1H, H-4′), 3.55 (m, 2H, H-5′). ^{13}C NMR (DMSO–d_6): δ 160.53 (C-4), 150.70 (C-2), 146.80 (C-6), 85.83 (C-4′), 75.35 (C-3′), 69.35/69.02 (C-5/C-1′), 63.44 (C-2′), 60.20 (C-5′). HRMS: $[M + H]^+$ calc. for $C_9H_{12}IN_2O_5$ 354.9791, found 354.9791.

(*E*)-5-(2-Bromovinyl)-1-(4-hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-1*H*,3*H*-pyrimidine-2,4-dione (5). To a solution of 500 mg (1.41 mmol) of **3** in 30 mL of dry CH_3CN were added 1.37 g (3.53 mmol) of trimethyl(2-tributylstannanylvinyl)silane and 150 mg (0.210 mmol) of $(Ph_3P)_2Pd(II)Cl_2$. The reaction mixture was stirred for 26 h at 50°C. The solvent was subsequently removed and the residue was purified by column chromatography (0–90% EtOAc/hexanes) yielding 298 mg (65%) of **4**. ^{1}H NMR (MeOH–d_4): δ 7.90 (s, 1H, H-6), 6.65 (d, 1H, J = 19.2 Hz, –CH═), 6.58 (d, 1H, J = 19.6 Hz, ═CHTMS), 4.95 (m, 1H, H-2′), 4.32 (dd, 1H, J = 3.2, 6.0 Hz, H-3′), 4.15 (dd, 1H, J = 6.9, 10.8 Hz, H_a-1′), 4.04 (dd, 1H, J = 3.2, 10.8 Hz, H_b-1′), 3.86 (dt, 1H, H-4′), 3.71 (m, 2H, H-5′), 0.08 (s, 9H, –TMS). A suspension of 56 mg (0.33 mmol) of XeF_2 and 28 mg (0.33 mmol) of LiBr in 7 mL of dry benzene under a nitrogen atmosphere was stirred for 10 min at 25°C. Then, 100 mg (0.306 mmol) of **4** was added and the reaction mixture was stirred for 48 h at 25°C. Next, 20 mL of CH_2Cl_2 was added, and the suspension was washed once with 2% $NaHSO_3$ solution and once with H_2O. Solvents were evaporated and the residue was purified by column chromatography (0–80% EtOAc/hexanes) to give 8 mg (8%) of **5**: mp 177°C. UV (MeOH): λ_{max} 297, 252 nm. ^{1}H NMR (MeOH–d_4): δ 7.86 (s, 1H, H-6), 7.32 (d, 1H, J = 13.5 Hz, –CH═), 6.79 (d, 1H, J = 13.5 Hz, ═CHBr), 4.94 (m, 1H, H-2′), 4.29 (dd, 1H, J = 2.4, 5.6 Hz, H-3′), 4.16 (dd, 1H, J = 6.7, 10.7 Hz, H_a-1′), 4.05 (dd, 1H, J = 2.9, 10.6 Hz, H_b-1′), 3.88 (dt, 1H, J = 1.8, 13.9 Hz, H-4′), 3.67–3.74 (m, 2H, H-5′). ^{13}C NMR (MeOH–d_4): δ 163.78 (C-4), 152.00 (C-2), 142.16 (CH═), 130.48 (C-6), 112.46 (C-5), 108.85 (═CHBr), 87.72 (C-4′), 77.89 (C-3′), 71.25 (C-1′), 65.74 (C-2′), 61.74 (C-5′). HRMS: $[M + H]^+$ calc. for $C_{11}H_{14}BrN_2O_5$ 333.0086, found 333.0070.

1-(4-Hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-(*E*)-5-(2-iodovinyl)-1*H*,3*H*-pyrimidine-2,4-dione (6). To a suspension of 220 mg (1.30 mmol) of XeF_2 in 7 mL of dry benzene under a nitrogen atmosphere was added 200 mg (1.33 mmol) of NaI. The mixture was stirred for 10 min at 25°C and then 63 mg (0.19 mmol) of **4** was added. The suspension was stirred for another 48 h at 25°C. Subsequently, 20 mL of CH_2Cl_2 was added and the suspension was washed once with 2% $NaHSO_3$ solution.

The aqueous layer was then extracted (2 ×) with EtOAc. The organic layers were combined and the solvents were evaporated. The resulting residue was purified by column chromatography (0–5% MeOH/$CHCl_3$) to yield 12 mg (17%) of **6**: mp 188°C. UV (MeOH): λ_{max} 301, 256 nm. ^{1}H NMR (MeOH–d_4): δ 7.85 (s, 1H, H-6), 7.29 (d, 1H, J = 14.8 Hz, –CH═), 7.12(d, 1H, J = 14.4 Hz, ═CHI), 4.93 (m, 1H, H-2′), 4.28 (dd, 1H, J = 2.8, 5.6 Hz, H-3′), 4.14 (dd, 1H, J = 6.8, 10.8 Hz, H_a-1′), 4.04 (dd, 1H, J = 3.2, 10.8 Hz, H_b-1′), 3.86 (dt, 1H, J = 2.0, 14.0 Hz, H-4′), 3.65-3.73 (m, 2H, H-5′). ^{13}C NMR (MeOH–d_4): δ 163.69 (C-4), 151.84 (C-2), 141.99 (CH═), 137.73 (C-6), 113.95 (C-5), 87.57 (C-4′), 78.58 (═CHI), 77.40 (C-3′), 71.12 (C-1′), 65.59 (C-2′), 61.57 (C-5′). HRMS: $[M + H]^+$ calc. for $C_{11}H_{14}IN_2O_5$ 380.9947, found 380.9929.

1-(4-Hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-5-vinyl-1*H*,3*H*-pyrimidine-2,4-dione (7). To a solution of 500 mg (1.41 mmol) of **3** in 30 mL of dry CH_3CN were added 150 mg (0.210 mmol) of $(Ph_3P)_2Pd(II)Cl_2$ and 1.0 g (3.2 mmol) of tributyl(vinyl)tin. The mixture was stirred for 26 h at 50°C. The solvent was then evaporated and the residue was purified by column chromatography (0–5% MeOH/$CHCl_3$) to afford 271 mg (75%) of **7**: mp 216°C (decomp.). UV (MeOH): λ_{max} 292, 238 nm. ^{1}H NMR (MeOH–d_4): δ 7.86 (br d, 1H, J = 1.6 Hz, H-6), 6.41 (dd, 1H, J = 11.6, 17.6 Hz, –CH═), 5.94 (dd, 1H, J = 1.6, 17.6 Hz, vinyl H_{trans}), 5.15 (dd, 1H, J = 1.6, 11.2 Hz, vinyl H_{cis}), 4.95 (m, 1H, H-2′), 4.32 (dd, 1H, J = 3.2, 6.0 Hz, H-3′), 4.16 (dd, 1H, J = 6.8, 10.4 Hz, H_a-1′), 4.04 (dd, 1H, J = 3.2, 10.4 Hz, H_b-1′), 3.86 (dt, 1H, J = 2.0, 13.6 HZ, H-4′), 3.67–3.75 (m, 2H, H-5′). ^{13}C NMR (MeOH–d_4): δ 164.47 (C-4), 152.29 (C-2), 140.92 (CH═), 129.40 (C-6), 115.66/113.77 (C-5/═CH_2), 87.53 (C-4′), 77.77 (C-3′), 71.29 (C-1′), 65.61 (C-2′), 61.78 (C-5′). HRMS: $[M + Li]^+$ calc. for $C_{11}H_{14}N_2O_5Li$ 261.1063, found 261.1065.

5-Ethynyl-1-(4-hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-1*H*,3*H*-pyrimidine-2,4-dione (8). To a solution of 500 mg (1.41 mmol) of **3** in 30 mL of dry CH_3CN were added 150 mg (0.210 mmol) of $(Ph_3P)_2Pd(II)Cl_2$ and 1.0 g (3.2 mmol) of tributyl(ethynyl)tin. The reaction mixture was heated for 24 h to 50°C. The solvent was then removed and the residue purified by column chromatography (0–5% MeOH/$CHCl_3$) affording 232 mg (65%) of **8**: mp 220°C (decomp.). UV (MeOH): λ_{max} 292, 228 nm. ^{1}H NMR (MeOH–d_4): δ 8.09 (s, 1H, H-6), 4.91 (m, 1H, H-2′), 4.27 (dd, 1H, J = 3.6, 5.6 Hz, H-3′), 4.15 (dd, 1H, J = 6.8, 10.8 Hz, H_a-1′), 4.04 (dd, 1H, J = 3.2, 10.8 Hz, H_b-1′), 3.83 (dt, 1H, J = 3.6, 9.2 Hz, H-4′), 3.66–3.72 (m, 2H, H-5′), 3.55 (s, 1H, ≡CH).^{13}C NMR (MeOH–d_4): δ 164.54 (C-4), 152.03 (C-2), 147.96 (C-6), 99.98 (C-5), 87.61 (C-4′), 83.16 (C≡), 77.76 (C-3′), 76.09 (≡CH), 71.04 (C-1′), 66.06 (C-2′), 61.85 (C-5′). HRMS: $[M + H]^+$ for $C_{11}H_{13}N_2O_5$ 253.0824, found 253.0827.

1-(4-Hydroxy-5-hydroxymethyl-tetrahydro-furan-3-yl)-5-phenyl-1*H*,3*H*-pyrimidine-2,4-dione (9). A solution of 500 mg (1.41 mmol) of **3**, 150 mg (0.210 mmol) of $(Ph_3P)_2Pd(II)Cl_2$, and 1.00 g (2.72 mmol) of tributyl(phenyl)tin in 30 mL of dry CH_3CN was heated for 18 h at 40°C and then for 4 h at 60°C. The suspension was then filtered through Celite® 545, and the filtrate was evaporated to dryness. The resulting residue was purified by column chromatography (0–4% MeOH/$CHCl_3$) yielding 161 mg (38%) of **9**: mp 213°C (decomp.). UV (MeOH) λ_{max} 289, 238 nm. ^{1}H NMR (MeOH-d_4): δ 7.94 (s, 1H, H-6), 7.54 (br d, 2H, J = 7.2 Hz, ortho Ph), 7.37 (t, 2H,

J = 7.6 Hz, meta Ph), 7.30 (t, 1H, J = 7.2 Hz, para Ph), 5.01 (m, 1H, H-2′), 4.38 (dd, 1H, J = 3.2, 5.6 Hz, H-3′), 4.19 (dd, 1H, J = 6.8, 10.8 Hz, H_a-1′), 4.10 (dd, 1H, J = 3.2, 10.8 Hz, H_b-1′), 3.83–3.89 (m, 1H, H-4′), 3.68–3.75 (m, 2H, H-5′). ^{13}C NMR (MeOH–d_4): δ 164.85 (C-4), 152.58 (C-2), 141.41 (C-6), 133.34 (phenyl), 129.51 (phenyl), 129.51 (phenyl), 129.11 (phenyl), 116.80 (C-5), 86.75 (C-4′), 77.39 (C-3′), 70.74 (C-1′), 65.36 (C-2′), 61.30 (C-5′). HRMS: $[M + H]^+$ calc. for $C_{15}H_{17}N_2O_5$ 305.1137, found 305.1125.

5-(3,3-Dimethylbut-1-ynyl)-1-(4-hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-1*H*,3*H*-pyrimidine-2,4-dione (10). To a solution of 500 mg (1.41 mmol) of **3**, 150 mg (0.210 mmol) of $(Ph_3P)_2Pd(II)Cl_2$, and 27 mg (0.41 mmol) of CuI in 10 mL of dry THF was added, over a period of 30 min, 348 mg (4.23 mmol) of 3,3-dimethylbut-1-yne in 10 mL of dry THF. The suspension was stirred for 18 h at 25°C. The solvent was then removed in vacuum and the residue was purified by column chromatography (0–6% MeOH/$CHCl_3$) to give 397 mg (91%) of **10**: mp 121°C. UV (MeOH): λ_{max} 297, 232 nm. ^{1}H NMR (MeOH–d_4): δ 7.89 (s, 1H, H-6), 4.91 (m, 1H, H-2′), 4.26 (dd, 1H, J = 3.7, 6.3 Hz, H-3′), 4.14 (dd, 1H, J = 6.6, 10.5 Hz, H_a-1′), 4.02 (dd, 1H, J = 3.8, 10.9 Hz, H_b-1′), 3.84 (dt, 1H, J = 2.5, 13.3 Hz, H-4′), 3.66-3.73 (m, 2H, H-5′), 1.27 (s, 9H, CH_3). ^{13}C NMR (MeOH–d_4): δ 164.47 (C-4), 151.94 (C-2), 145.54 (C-6), 103.19 (≡C), 101.47 (C-5), 87.21 (C-4′), 77.42 (C-3′), 71.42 (5-U-C≡), 70.85 (C-1′), 65.62 (C-2′), 61.70 (C-5′), 31.24 (CH_3), 29.12 (CMe_3). HRMS: $[M + H]^+$ calc. for $C_{15}H_{21}N_2O_5$ 309.1450, found 309.1462.

3-(4-Hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-6-methoxymethyl-3*H*-furo[2,3-d]pyrimidin-2-one (11). To a solution of 500 mg (1.41 mmol) of **3**, 150 mg (0.210 mmol) of $(Ph_3P)_2Pd(II)Cl_2$, and 27 mg (0.14 mmol) of CuI in 10 mL of anhydrous THF and 0.29 mL of dry Et_3N was added dropwise, over a period of 30 min, a solution of 296 mg (4.23 mmol) of 3-methoxypropyne in 10 mL of anhydrous THF. The mixture was heated for 2 d at 70°C and then filtered through Celite® 545. Solvents were evaporated and the resulting residue was purified by column chromatography (0–5% MeOH/$CHCl_3$) to give 120 mg (29%) of the bicyclic compound **11**: mp 196°C. UV (MeOH): λ_{max} 332, 229 nm. ^{1}H NMR (MeOH–d_4): δ 8.63 (s, 1H, H-4), 6.68 (s, 1H, H-3), 5.14 (m, 1H, H-2′), 4.32 (dd, 1H, J = 2.0, 5.6 Hz, H-3′), 4.27 (dd, 1H, J = 6.0, 10.8 Hz, H_a-1′), 4.22 (dd, 1H, J = 2.4, 10.8 Hz, H_b-1′), 3.85 (dd, 1H, J = 2.4, 12.4 Hz, H_a-5′), 3.78 (m, 1H, H-4′), 3.71 (dd, 1H, J = 3.6, 12.0 Hz, H_b-5′), 3.39 (s, 3H, $-OCH_3$). ^{13}C NMR (MeOH–d_4): δ 172.81 (N═C), 156.67/156.01 (C═O/O–C═), 142.40 (N–C═), 108.88 (═C), 104.79 (CH═), 88.43 (C-4′), 78.79 (C-3′), 71.60 (C-1′), 68.76 (CH_2OMe), 67.23 (C-2′), 61.93 (C-5′), 58.83 (OCH_3). HRMS: $[M + H]^+$ calc. for $C_{12}H_{17}N_2O_6$ 297.1086, found 297.1091.

1-(4-Hydroxy-5-hydroxymethyltetrahydrofuran-3-yl)-5-(3-methoxyprop-1-ynyl)-1*H*,3*H*-pyrimidine-2,4-dione (12). A solution of 500 mg (1.41 mmol) of **3**, 150 mg (0.210 mmol) of $(Ph_3P)_2Pd(II)Cl_2$, 296 mg (4.23 mmol) of 3-methoxypropyne, and 81 mg (0.42 mmol) of CuI in 7 mL (3–5 mL/mmol of substrate) of dry DMF and 0.40 mL (2.8 mmol) of dry Et_3N was stirred for 2 h at 25°C. The solvents were then removed and the resulting residue was purified by column chromatography (0–6% MeOH/$CHCl_3$) to yield 288 mg (69%) of **12**: mp 179°C. UV (MeOH): λ_{max} 295, 232

nm. ^{1}H NMR (MeOH–d_4): δ 8.06 (s, 1H, H-6), 4.91 (m, 1H, H-2′), 4.25-4.29 (m, 3H, H-3′, –$\underline{CH_2}$OMe), 4.15 (dd, 1H, J = 6.4, 10.4 Hz, H_a-1′), 4.05 (dd, 1H, J = 3.2, 10.4 Hz, H_b-1′), 3.84 (dt, 1H, J = 3.6, 13.2 Hz, H-4′), 3.66–3.73 (m, 2H, H-5′), 3.38 (s, 3H, –OCH_3). ^{13}C NMR (MeOH–d_4): δ 164.29 (C-4), 151.85 (C-2), 147.29 (C-6), 100.02 (C-5), 90.19 (≡C), 87.48 (C-4′), 78.73 (5-U-C≡), 77.63 (C-3′), 70.91 (C-1′), 65.88 (C-2′), 61.70 (C-5′), 61.01 (CH_2OMe), 57.83 (OCH_3). HRMS: $[M + H]^+$ calc. for $C_{13}H_{17}N_2O_6$ 297.1086, found 297.1084.

ACKNOWLEDGMENTS

The project described was supported by Grant Number AI 32851 from the National Institutes of Health. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Some aspects of this work were initiated at the University of Iowa prior to our move to the University of Georgia. We thank the Nebraska Center for Mass Spectrometry at the University of Nebraska-Lincoln for the HRMS data.

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Received August 26, 2003
Accepted October 6, 2003

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