Synthesis of 5-(Acylethynyl)uracils and their Corresponding 2'-Deoxyribonucleosides through Palladium-catalysed Reactions[1]

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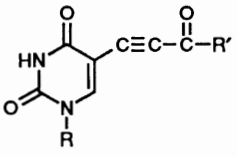
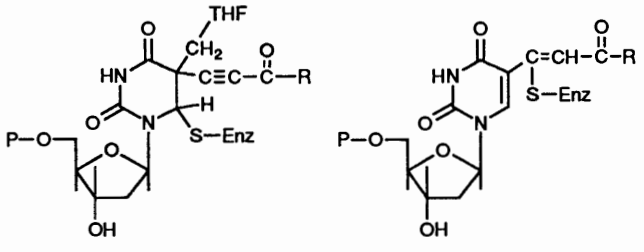
Good yields of the title uracils were obtained by using the palladium-catalysed reaction between 5-iodo-2,4-dimethoxypyrimidine and substituted propargylic alcohols rather than the corresponding ketones. The same strategy works for coupling with the 5-iodo-2'-deoxyuridines.

5-Substituted uracil derivatives have proved to be of interest and use in cancer[2] and viral chemotherapy,[3–8] as enzyme inhibitors[9,10] and in the synthesis of modified nucleotides.[11,12] Our interest was in producing potential anticancer and antiviral compounds bearing conjugated acetylenic ketones of structures **I** and **II**.[13]



I R = H, R' = Ar
II R = 2'-deoxy-D-*erythro*-pentofuranose, R' = Ar

In these compounds [after their conversion into the corresponding 2'-deoxyribonucleotides †], the stereoelectronic characteristics of the C-5 substituents were expected to facilitate the attack of the thiol group of the cysteine moiety of the enzyme thymidylate synthase (TS),[14] a critical enzyme needed for cellular multiplication, at the C-6 position of the uracil ring, leading to tight enzyme inhibitor complexes (**A** and **B**).[15] Thus,



A **B**

these compounds were expected to act as effective inhibitors of the TS enzyme and to have antitumour properties. These expectations have been fulfilled to some extent. The lead compound, 5-(*p*-toluoylethynyl)uracil **I** (R = H, R' = *p*-tolyl), was found to be highly active against both L1210/0 mouse leukaemia and CCRF-CEM human lymphoblastoid cells *in vitro*. It also inhibited the TS enzyme.[16] In view of the success of 5-(acylethynyl)uracils (AEUs) as antitumour agents and as inhibitors of TS enzyme, we became interested in the development of the corresponding 2'-deoxyribonucleosides **II** which, we believe, will have stronger antitumour and TS-enzyme-inhibitory properties. In this paper, we describe an improved method for the synthesis of both the AEUs and the corresponding 2'-deoxyribonucleosides.

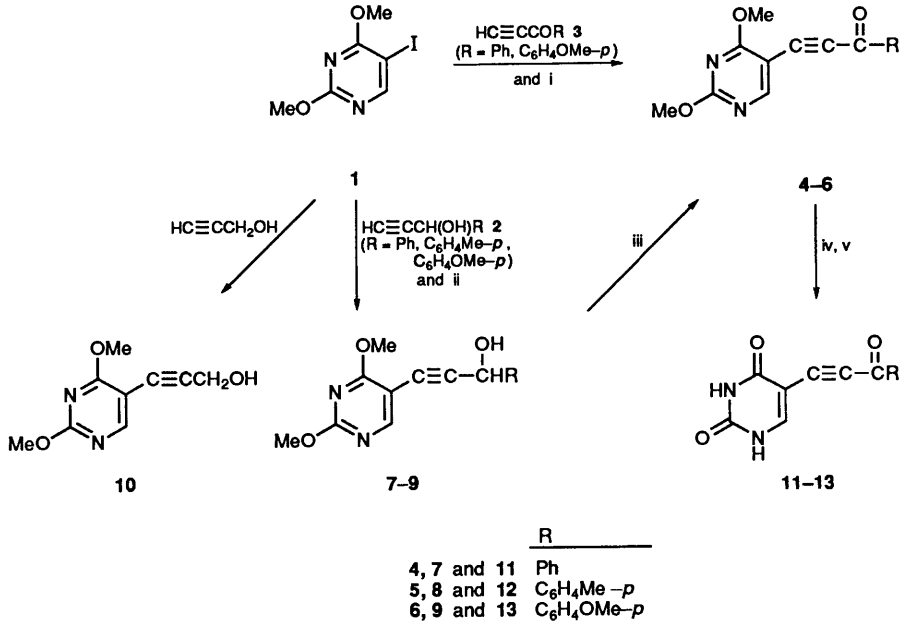
† Strictly speaking, these should be called 2'-deoxy-D-*erythro*-pentofuranonucleotides.

Results and Discussion

Previously, we have reported two general methods for the synthesis of AEUs.[15,16] However, these methods suffer from the disadvantages of involving long reaction sequences, being time consuming, and having poor overall yields (10–25%). Also, they could not be adapted to the synthesis of the corresponding 2'-deoxyribonucleosides. Thus, we were prompted to develop an alternative method for the synthesis of the AEUs and the corresponding 2'-deoxyribonucleosides.

Palladium-catalysed reactions have been developed by Heck and co-workers for carbon–carbon bond formation,[17] and have been utilised by various investigators for carboannulation[18] and heteroannulation processes.[19] The application of this useful reaction for the synthesis of 5-substituted uracil nucleosides was first reported by Bergstrom[20] and since then has been used by him and other investigators for the synthesis of a number of uracil nucleosides with vinylic moieties or the corresponding saturated entities at the C-5 position of the uracil ring.[21] The attachment of alkynyl substituents to aromatic and heterocyclic rings through palladium-catalysed reaction of acetylenic substrates has been reported by other investigators.[22] A number of 5-alkynyluracil nucleosides have also been synthesized by coupling of terminal alkynes with 5-iodouracil nucleosides in the presence of palladium catalysts.[23]

In our attempt towards the palladium-mediated synthesis of AEUs, we started with 5-iodo-2,4-dimethoxypyrimidine **1** as the starting material (Scheme 1). 5-Iodo-2,4-dimethoxypyrimidine was used instead of 5-iodouracil due to the poor solubility of the latter in most organic solvents, and was obtained either by direct iodination of 2,4-dimethoxypyrimidine with *N*-iodosuccinimide in trifluoroacetic acid–trifluoroacetic anhydride[24] or from 5-iodouracil by the procedure of Prystaš and Šorm.[25] The other components for the coupling reaction, *e.g.* the acetylenic ketones **3**, were obtained by the oxidation[26] of the corresponding acetylenic alcohols **2** which were synthesized according to the procedure of Jones and McCombie.[27] The acetylenic ketones were condensed with 5-iodo-2,4-dimethoxypyrimidine in the presence of bis(triphenylphosphine)-palladium(II) chloride, copper(I) iodide and sodium hydrogen carbonate in acetonitrile at 50 °C to give 5-(acylethynyl)-2,4-dimethoxypyrimidines **4** and **6** in 15–19% yield. The poor yields in the palladium-catalysed reaction could be attributed to the polymerisation of the acetylenic ketones under the reaction conditions. The use of other solvents [dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and Et_3N] and bases (Et_3N) did not improve the yields. In order to obviate the problems associated with polymerisation of acetylenic ketones, we condensed 5-iodo-2,4-dimethoxypyrimidine with the acetylenic alcohols **2** in the presence of bis(triphenylphosphine)-palladium(II) chloride and copper(I) iodide in stirred triethylamine at 55 °C for 6 h. Although there was some dimeris-



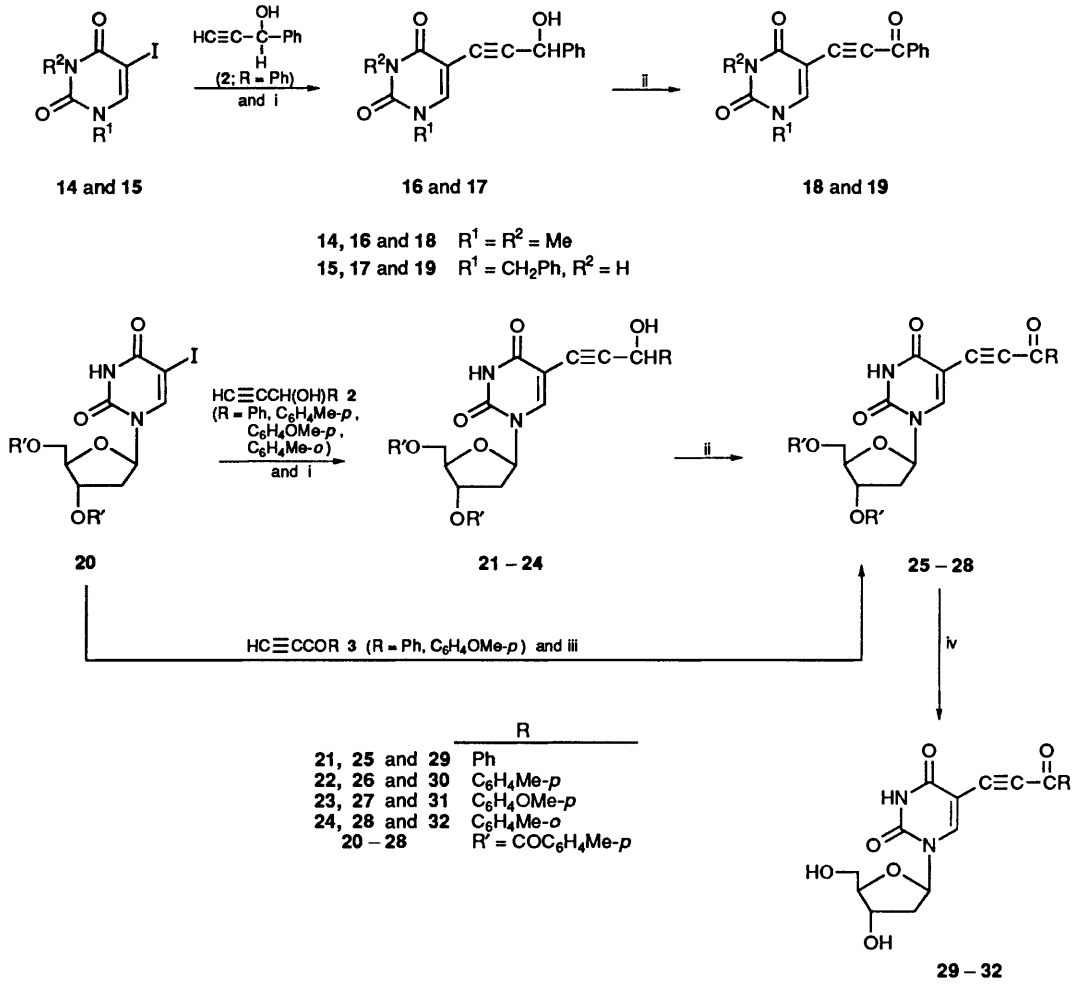
Scheme 1 *Reagents and conditions:* i, $(PPh_3)_2PdCl_2$, CuI, $NaHCO_3$ in MeCN, 50 °C; ii, $(PPh_3)_2PdCl_2$, CuI, Et_3N, 55 °C; iii, MnO_2, Ch_2Cl_2; iv, 6 mol dm^{-3}, HCl; v, NaOH in 95% EtOH

ation[28] of the acetylenic alcohols, excellent yields (85–99%) of 5-(3-aryl-3-hydroxyalkynyl)-2,4-dimethoxypyrimidines **7–9** were obtained under the reaction conditions. It appears that condensation of the acetylenic alcohols with 5-iodo-2,4-dimethoxypyrimidine was faster under palladium catalysis than was the self-dimerisation of the acetylenic alcohols. When propargyl alcohol (prop-2-yn-l-ol) was condensed with compound **1** under palladium catalysis, 5-(3-hydroxyprop-2-ynyl)-2,4-dimethoxypyrimidine **10** was obtained in a somewhat lower yield (63%). Compounds **7–10** were well characterised by their IR absorption at 3260 and 2200 cm^{-1} (weak, C≡C), UV absorption maxima at 280 nm, and their characteristic ^1H NMR spectra. They were identical with those reported earlier.[15] The alcohols **7–9** were found to be susceptible to slow aerial oxidation. Oxidation of the alcohols **7–9** with manganese dioxide in dichloromethane led to the corresponding ketones **4–6**, which were identical with those synthesized directly by coupling of 5-iodo-2,4-dimethoxypyrimidine with the acetylenic ketones **3**. The synthesis of the ketones **4–6** by an alternative route and their conversion into AEUs **11–13** have also been reported by us.[15] The palladium-catalysed procedure for the synthesis of AEUs **11–13** was, however, found to be much superior (overall yields 40–45% based on 5-iodo-2,4-dimethoxypyrimidine) to the Grignard procedure[15] for the synthesis of ynones **11–13** (overall yields 16–20% based on substrate **1**) or to the silicon-mediated synthesis[13] for ynones **11–13** (overall yields 7–9% based on 5-acetyluracil).

In our efforts towards the synthesis of 2′-deoxyribonucleosides of AEUs **11–13**, we successfully silylated compounds **11–13** with hexamethyldisilazane and chlorotrimethylsilane. However, the condensation of the silyl derivatives with 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-α-D-*erythro*-pentofuranosyl chloride under various conditions[29] failed. The reason could be the weaker nucleophilicity of the N-1 nitrogen atom, due to the presence of an electron-withdrawing group at C-5 of the uracil moiety. We therefore turned to the palladium-catalysed reaction for the synthesis of the 2′-deoxyribonucleosides and this was accomplished according to Scheme 2. 5-Iodo-N^1,N^3-dimethyluracil **14** and N^1-benzyl-5-iodouracil **15** were studied as model compounds. Their condensation with 1-phenylprop-2-yn-1-ol **2** (R = Ph) in the presence of bis(triphenylphosphine)palladium(II) chloride, copper(I) iodide and triethylamine in DMF took place readily to yield compounds **16** and **17**, respectively, in excellent yield. These compounds were oxidised with pyridinium chlorochromate (PCC)[30] to afford the corresponding ketones, *viz.* 5-(benzoylethynyl)-N^1,N^3-dimethyluracil **18** and 5-(benzoylethynyl)-N^1-benzyluracil **19**.

The condensation of 5-iodo-3′,5′-di-*O*-(*p*-toluoyl)-2′-deoxyuridine **20** with the acetylenic ketones **3** (R = Ph, C_6H_4OMe-*p*) was accomplished in the presence of catalytic amounts of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide in the presence of sodium hydrogen carbonate as a base in stirred acetonitrile at 50 °C for 8 h. However, the yields of the condensation products **25** and **27** were extremely poor (~ 20%). However, 5-iodo-3′,5′-di-*O*-(*p*-toluoyl)-2′-deoxyuridine **20** readily condensed with the acetylenic alcohols **2** in the presence of bis(triphenylphosphine)palladium(II) chloride, copper(I) iodide and triethylamine in DMF. The yields of the condensation products were found to be excellent, *viz.* **21** (92%), **22** (93%), **23** (88%) and **24** (83%). In the IR spectra, the condensation products **21–24** showed absorption at ~3440 (hydroxy group), 1720 (conjugated carbonyl) and 1660 (ureido) cm^{-1}. No absorption for the acetylenic triple bond could be seen. In the UV spectra, the compounds exhibited absorption maxima between 285 and 291 nm. In the ^1H NMR spectra, these compounds exhibited a multiplet at δ 2.08–2.96 (due to 2′-H_2), a multiplet at δ ~ 4.40–4.88 (due to 4′- and 5′-H_2) and another multiplet at δ 5.44–5.74 (due to 3′-H and side-chain 3-H). The 1′-hydrogen exhibited a double doublet at δ 6.24–6.48, indicating the β-configuration for the nucleosides. The aromatic protons exhibited signals at appropriate positions (see Experimental section).

The acetylenic alcohols **21–24** were readily oxidised with PCC in dichloromethane to the corresponding ketones, 5-(acylethynyl)-3′,5′-di-*O*-(*p*-toluoyl)-2′-deoxyuridines **25–28**. These were obtained as solids after column chromatography on silica gel and were identical with the samples previously obtained by the direct condensation of iodide **20** with the acetylenic ketones **3** under palladium-catalysed conditions. In contrast to the acetylenic alcohols **21–24**, the ketones **25–28** exhibited strong absorption at ~2200 cm^{-1} due to the



Scheme 2 *Reagents:* i, $(PPh_3)_2PdCl_2$, CuI, Et_3N, DMF; ii, PCC, CH_2Cl_2; iii, $(PPh_3)_2PdCl_2$, CuI, $NaHCO_3$, MeCN; iv, NaOMe, MeOH

conjugated acetylenic group. In the UV spectra, the compounds showed absorption maxima between 323 and 333 nm. In the ^1H NMR spectra, the ketones **25–28** exhibited a multiplet at δ 2.08–2.96 (2'-H_2), a multiplet at δ 4.40–4.96 (4' and 5'-H_2) and a double doublet at δ 6.16–6.48 (1'-H). 5-(Acylethynyl)-3',5'-di-*O*-(*p*-toluoyl)-2'-deoxyuridines **25–28** on treatment with sodium methoxide in methanol were smoothly converted into the target compounds, the 5-(acylethynyl)-2'-deoxyuridines **29–32**. These were characterised by their elemental analyses, IR absorption at 2200 cm^{-1} (conjugated acetylenic group), UV absorption maxima at 325–335 nm, and their ^1H NMR spectra (see Experimental section).

In conclusion, we report for the first time the condensation of conjugated acetylenic ketones with iodopyrimidines and 5-iodouracil nucleosides under palladium-catalysed conditions, which proceeded in only poor yield. However, a two-step procedure involving reaction of acetylenic alcohols with iodopyrimidines or 5-iodouracil nucleosides under palladium catalysis and subsequent oxidation of the products with PCC led to the pyrimidine- or uracil-substituted conjugated acetylenic ketones in excellent yield. Thus, the process has yielded 5-(acylethynyl)uracils and their corresponding 2'-deoxyribonucleosides in good yield. 5-(Acylethynyl)uracils **11–13** were found to be active against CCRF-CEM human lymphoblastoid cells and L1210/0 mouse leukaemia cells in culture. They were also inhibitors of the TS enzyme.[16] Biological and biochemical studies on 5-(acylethynyl)-2'-deoxy uridines **29–32** are in progress.

Experimental

M.p.s were determined on a Reichert 285980 (Austria) m.p.-bath and are uncorrected. UV spectra were recorded on a Hitachi 200–20 spectrometer for solutions in spectrophotometric-grade ethanol (Baker). IR spectra were taken on a Perkin-Elmer 298 instrument for samples on KBr plates. ^1H NMR spectra were recorded on a Varian XL-200 spectrometer, a 100 MHz FX-100 spectrometer, or on a 60 MHz EM 360L spectrometer, for samples in solvents as indicated, with tetramethylsilane as internal standard, *J* values being in Hz. Silica gel TLC was performed on 60F-254 precoated sheet (E. Merck) and column chromatography was done on silica gel (60–120 mesh). Elemental analyses were performed on a Perkin-Elmer elemental analyser 240 C. All solvents and reagents were reagent-grade materials and were further purified by conventional methods. (+)-5-Iodo-2'-deoxyuridine was obtained from Aldrich Chemical Co., Milwaukee, Wisconsin USA.

The 1-arylprop-2-yn-1-ols **2** were synthesized according to the published procedures.[27] The 1-arylprop-2-yn-1-ones **3** were synthesized by oxidation of the corresponding alcohols with Jones' reagent.[26]

Synthesis of 5-(3-*Aryl*-3-*hydroxyprop*-1-*ynyl*)-2,4-*dimethoxypyrimidines by Palladium-catalysed Reactions.—Typical procedure:* 5-(3-*hydroxy*-3-*phenylprop*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **7**. A mixture of 5-iodo-2,4-dimethoxypyrimidine **1**[24] (300 mg, 1.12 mmol), bis(triphenyl phosphine)palladium(II) chloride (10 mg, 0.014 mmol) and copper(I) iodide (10 mg, 0.05 mmol) in

triethylamine (10 cm^3) was stirred under nitrogen for 30 min. 1-Phenylprop-2-yn-1-ol (180 mg, 1.36 mmol) was then added to the mixture and this was further stirred at 55–60 °C for 6 h, when TLC indicated complete disappearance of the starting material. The residue, obtained after removal of triethylamine, was treated with water (75 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined extracts were washed with water (3 × 50 cm^3) and dried (Na_2SO_4). After evaporation of the solvent a brown gum was obtained, which was purified by chromatography on a column of silica gel (60–120 mesh; chloroform eluent) to afford 5-(3-hydroxy-3-phenylprop-1-ynyl)-2,4-dimethoxypyrimidine **7** (260 mg, 85%) as gum, identical with an authentic sample[15] from spectroscopic (IR, UV, ^1H NMR) comparisons.

5-[3-*Hydroxy*-3-(p-*tolyl*)*prop*-1-*ynyl*]-2,4-*dimethoxypyrimidine* **8**. This was synthesized according to the above procedure from 5-iodo-2,4-dimethoxypyrimidine **1** (1 g, 3.76 mmol), bis(triphenylphosphine)palladium(II) chloride (30 mg, 0.042 mmol), copper(I) iodide (25 mg, 0.13 mmol) and 1-(*p*-tolyl)prop-2-yn-1-ol (660 mg, 4.52 mmol) to yield compound **8** after column chromatography (SiO_2, 60–120 mesh) as a light brown solid (1 g, 94%), which was crystallised from diethyl ether–light petroleum (40–60 °C) to give a solid, m.p. 108 °C (lit.,[15] 110 °C). This was identical with an authentic sample[15] from IR, UV and ^1H NMR spectroscopic comparisons.

5-[3-*Hydroxy*-3-(p-*methoxyphenyl*)*prop*-1-*ynyl*]-2,4-*dimethoxypyrimidine* **9**. This was synthesized, by following the procedure as for compounds **7** and **8**, from 5-iodo-2,4-dimethoxypyrimidine **1** (2 g, 7.52 mmol), bis(triphenylphosphine)palladium(II) chloride (60 mg, 0.085 mmol), copper(I) iodide (50 mg, 0.26 mmol) and 1-*p*-methoxyphenyl)prop-2-yn-1-ol (1.80 g, 11.1 mmol) to yield compound **9** (2.24 g, 99%) after chromatography (SiO_2, 60–120 mesh), and which was crystallised from diethyl ether–light petroleum (60–80 °C) to a solid, m.p. 117 °C (lit.,[15] 116–117 °C), identical with an authentic sample[15] from spectroscopic comparisons.

5-(3-*Hydroxyprop*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **10**. This was synthesized from 5-iodo-2,4-dimethoxypyrimidine **1** (1 g, 3.76 mmol), propargyl alcohol (280 mg, 5 mmol), bis(triphenylphosphine)palladium(II) chloride (30 mg, 0.043 mmol) and copper(I) iodide (25 mg, 0.13 mmol). After purification by chromatography (SiO_2, 60–120 mesh), compound **10**, a solid (460 mg, 63%), was obtained, which was crystallised from light petroleum (60–80 °C), m.p. 124 °C (lit.,[15] 120–122 °C), identical with an authentic sample from spectroscopic comparisons.

Synthesis of 5-(*Acylethynyl*)-2,4-*dimethoxypyrimidines* **4–6**—. *Method A: Oxidation of compounds* **7–9** *to the corresponding ketones* **4–6** *with manganese dioxide.* See ref. 15.

Method B: Palladium-catalysed reaction. Synthesis of 5-(*benzoylethynyl*)-2,4-*dimethoxypyrimidine* **4**. A mixture of 5-iodo-2,4-dimethoxypyrimidine **1** (260 mg, 0.98 mmol) in acetonitrile (10 cm^3), bis(triphenylphosphine)palladium(II) chloride (10 mg, 0.014 mmol) and copper(I) iodide (10 mg, 0.05 mmol) was stirred under nitrogen for 15 min. 1-Phenylprop-2-yn-1-one (250 mg, 1.92 mmol) was then added to the mixture, followed by addition of sodium hydrogen carbonate (100 mg, 1.2 mmol) after 15 min. The whole mixture was then stirred at room temperature (30 °C) for 1 h and at 50 ° for 8 h. The solvent was then removed under reduced pressure to yield a black residue, which was treated with water (50 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined extracts were washed successively with disodium EDTA (10%; 3 × 50 cm^3) and water (3 × 50 cm^3) and dried (anhydrous sodium sulfate). After removal of solvent, the residue was purified by chromatography [SiO_2, 60–120 mesh; eluent 10% ethyl acetate in light petroleum (60–80 °C), followed by chloroform] to yield compound **4** as a solid (40 mg, 15%), which was crystallised from methanal to give a solid, m.p. 125 °C (lit.,[15] 124–125 °C), identical with an authentic sample[15] from spectroscopic comparisons.

2,4-*Dimethoxy*-5-(p-*methoxybenzoylethynyl*)*pyrimidine* **6**. This was obtained in 19% yield from 5-iodo-2,4-dimethoxypyrimidine **1** (240 mg, 0.90 mmol), bis(triphenylphosphine)-palladium(II) chloride (10 mg, 0.014 mmol), copper(I) iodide (10 mg, 0.05 mmol), 1-(*p*-methoxyphenyl)prop-2-yn-1-one (300 mg, 1.87 mmol) and sodium hydrogen carbonate (100 mg, 1.20 mmol) by following the procedure for compound **4**; m.p. 135 °C (lit.,[15] 136 °C).

5-(3-*Hydroxy*-3-*phenylprop*-1-*ynyl*)-N^1,N^3-*dimethyluracil* **16**. A solution of 5-iodo-N^1,N^3-dimethyuracil **14**[24] (270 mg, 1.0 mmol) in DMF (10 cm^3), bis(triphenylphosphine)palladium(II) chloride (30 mg, 0.043 mmol) and copper(I) iodide (30 mg, 0.16 mmol) was stirred under nitrogen for 15 min. 1-Phenylprop-2-yn-1-ol (260 mg, 1.97 mmol) and triethylamine (200 mg, 1.98 mmol) were then added and the mixture was further stirred at 50 °C for 6 h. After removal of solvent, the residue was treated with water (50 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined extracts were washed with water (3 × 50 cm^3), dried (anhydrous sodium sulfate), and the solvent was removed to yield a brown gum, which was purified by chromatography (SiO_2, 60–120 mesh; eluent 4% methanol in chloroform) to afford *compound* **16** as a solid (250 mg, 91%), which was crystallised from methanol, m.p. 203–204 °C (Found: C, 66.5; H, 5.45; N, 10.6. $C_{15}H_{14}N_2O_3$ requires C, 66.65; H, 5.2; N, 10.4%); ν_{max}/cm^{-1} 3400, 2230, 1690 br and 1633 br; λ_{max}/nm 295 (ε 15 480) and 233 (15 770); δ [($^2H_6$) DMSO + $CDCl_3$; 60 MHz] 3.33 (3 H, s, 1-Me), 3.39 (3 H, s, 3-Me), 5.60 (1 H, d, *J* 6, OH), 5.79 (1 H, d, *J* 6, C*H*OH), 7.26–7.73 (5 H, m, ArH) and 7.79 (1 H, s, 6 – H).

5-(*Benzoylethynyl*)-N^1,N^3-*dimethyluracil* **18**. To a solution of 5-(3-hydroxy-3-phenylprop-1-ynyl)-N^1,N^3-dimethyluracil **16** (100 mg, 0.37 mmol) in dichloromethane (25 cm^3) was added PCC (640 mg, 2.97 mmol). The mixture was stirred at room temperature (30 °C) for 2 h, filtered, and the residue was washed with dichloromethane (3 × 10 cm^3). The combined filtrates, on evaporation of solent, furnished a solid, which was purified by chromatography on a short column of silica gel (25% ethyl acetate in chloroform as eluent) (90 mg, 90%) and recrystallised from methanol to give *compound* **18** as a solid, m.p. 275 °C (Found: C, 66.8; H, 4.5; N, 10.3. $C_{15}H_{12}N_2O_3$ requires C, 67.15; H, 4.5; N, 10.4%); ν_{max}/cm^{-1} 2200vs, 1705, 1660, 1640 and 1620; λ_{max}/nm 332 (ε 22 040) and 265 (11 610); δ ([$^2H_6$]DMSO; 60 MHz) 3.30 (3 H, s, 1-Me), 3.46 (3 H, s, 3-Me), 7.59–7.89 (3 H, m, $ArH_{m,p}$) 8.16–8.46 (2 H, m, ArH_o) and 8.76 (1H, s, 6-H).

N^1-*Benzyl*-5-*iodouracil* **15**. A mixture of the potassium salt of 5-iodouracil [made by stirring of 5-iodouracil (6 g, 25.21 mmol) and anhydrous potassium carbonate (3.6 g, 26.08 mmol) in DMF (75 cm^3) for 2 days at room temperature] and benzyl bromide was stirred at room temperature for 6 days. After removal of solvent under reduced pressure and work-up, a semi-solid mass was obtained. This was chromatographed on a column of silica gel (60–120 mesh) to yield N^1, N^3-dibenzyl-5-iodouracil (eluent chloroform) (4.4 g, 42%), m.p. 104–105 °C (lit.,[24] 102–104 °C) and N^1-*benzyl*-5-*iodouracil* **15** (eluent 25% ethyl acetate in chloroform) (2.2 g, 26%), which was crystallised from methanol, m.p. 216–217 °C (Found: C, 40.5; H, 3.0. $C_{11}H_9IN_2O_2$ requires C, 40.3; H, 2.8%); ν_{max}/cm^{-1} 1715, 1670 and 1610; λ_{max}/nm 292 (ε 10 075); δ ([$^2H_6$]DMSO + $CDCl_3$; 60 MHz) 4.92 (2 H, s, 1-CH_2), 7.36 (5 H, s, ArH) and 7.89 (1 H, s, 6-H).

5-(*Benzoylethynyl*)-N^1-*benzyluracil* **19**. A mixture of N^1-benzyl-5-iodouracil (330 mg, 1 mmol), bis(triphenylphosphine)-palladium(II) chloride (70 mg, 0.1 mmol), copper(I) iodide (40 mg, 0.21 mmol), 1-phenylprop-2-yn-1-ol (270 mg, 2 mmol) and triethylamine (200 mg, 1.98 mmol) in DMF (10 cm^3) was stirred

at 50 °C under nitrogen for 6 h. After removal of solvent, the residue, on work-up and purification by chromatography (SiO_2, 60–120 mesh; eluent 4% methanol in chloroform), yielded N^1-benzyl-5-(3-hydroxy-3-phenylprop-1-ynyl)uracil **17** as a gum (280 mg, 84%). A portion of compound **17** (100 mg, 0.3 mmol) was oxidised with PCC (650 mg, 3.02 mmol) in dichloromethane (10 cm^3) stirred at room temperature for 2 h. After work-up and purification by column chromatography, a light yellow solid (70 mg, 70%) was obtained, which was crystallised from methanol to give *compound* **17** as a solid, m.p. 210 °C (Found: C, 72.6; H, 4.3; N, 8.6. $C_{20}H_{14}N_2O_3$ requires C, 72.8; H, 4.3; N, 8.5%); ν_{max}/cm^{-1} 2210, 1715, 1685, 1640 and 1620; λ_{max}/nm 331 (ε 23 290) and 266 (12 720); δ([$^2H_6$]DMSO; 60 MHz) 5.07 (2 H, s, benzylic H), 7.43 (5 H, m, ArH), 7.56–7.86 (3 H, m, $ArH_{m,p}$), 8.16–8.43 (2 H, m, ArH_o) and 8.86 (1 H, s, 6-H).

Synthesis of 5-(3-*Aryl*-3-*hydroxyprop*-1-*ynyl*)-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridines*.—*Typical procedure: Synthesis of* 5-(3-*hydroxy*-3-*phenylprop*-1-*ynyl*)-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridine* **21**. Bis(triphenylphosphine)palladium(II) chloride (40 mg, 0.057 mmol) and copper(I) iodide (20 mg, 0.10 mmol) were added to a magnetically stirred solution of 5-iodo-3′,5′-di-*O*-(*p*-toluoyl)-2′-deoxyuridine **20** (280 mg, 0.47 mmol) in DMF (10 cm^3) under nitrogen. After 15 min, 1-phenylprop-2-yn-1-ol (150 mg, 1.13 mmol) was added to the mixture, followed by addition of triethylamine (100 mg, 0.99 mmol). The mixture was then heated at 50 °C for 5 h. After removal of solvent under reduced pressure, the residue was dissolved in chloroform. The chloroform solution was washed successively with 10% aq. disodium EDTA (3 × 50 cm^3) and water (3 × 50 cm^3) and was dried (anhydrous Na_2SO_4). After removal of solvent, the residue was purified by column chromatography (SiO_2, 60–120 mesh; eluent 4% methanol in chloroform) to yield 5-(3-*hydroxy*-3-*phenylprop*-1-*ynyl*)-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridine* **21** (260 mg, 92%) which was crystallised from chloroform–methanol to give a solid, m.p. 205–206 °C (Found: C, 68.7; H, 5.0; N, 5.0. $C_{34}H_{30}N_2O_8$ requires C, 68.7; H, 5.1; N, 4.7%); ν_{max}/cm^{-1} 3420 br, 1720, 1710, 1660 and 1610; λ_{max}/nm 285 (ε 14 790) and 239 (42 660); δ($CDCl_3$; 100 MHz), 2.08–2.92 (2 H, m, 2′-H_2), 2.32 (3 H, s, ArMe), 2.44 (3 H, s, Ar*Me*), 4.52–4.62 (1 H, m, 4′-H), 4.62–4.80 (2 H, m, 5′-H_2), 5.44–5.68 (2 H, m, 3′- and side-chain 3-H), 6.24–6.44 (1 H, dd, 1′-H), 7.08–7.64 (9 H, m, ArH), 7.80–8.04 (5 H, m, ArH and 6-H) and 8.68 (1 H, br s, NH).

5-[3-*Hydroxy*-3-(p-*tolyl*)*prop*-1-*ynyl*]-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridine* **22**. This was synthesized by following the above procedure, from compound **20** (280 mg, 0.47 mmol), bis(triphenylphosphine)palladium(II) chloride (40 mg, 0.056 mmol), copper(I) iodide (20 mg, 0.10 mmol), 1-(*p*-tolyl)prop-2-yn-1-ol (140 mg, 0.95 mmol) and triethylamine (100 mg, 0.99 mmol) in DMF (10 ml). After work-up and purification, a foam (270 mg, 93%) was obtained, which was crystallised from chloroform–diethyl ether to give *compound* **22**, m.p. 218–219 °C (Found: C, 69.1; H, 5.7; N, 4.8. $C_{35}H_{32}N_2O_8$ requires C, 69.1; H, 5.30; N, 4.60%); ν_{max}/cm^{-1} 3450 br, 1720, 1710, 1665 and 1610w; λ_{max}/nm 291 (ε 15 140) and 239 (44 670); δ($CDCl_3$; 270 MHz) 2.26 (1 H, m, 2′-H), 2.32 (6 H, s, Ar*Me*), 2.43 (3 H, s, Ar*Me*), 2.78 (1 H, m, 2′-H), 4.55–4.82 (3 H, m, 4′-H and 5′-H and 5′-H_2), 5.47 (1 H, s, C*H*OH), 5.58 (1 H, m, 3′-H), 6.36 (1 H, dd, *J* 5.67 and 8.48, 1′-H), 7.10–7.96 (13 H, m, ArH and 6-H) and 8.14 (1 H, s, NH).

5-[3-*Hydroxy*-3-(p-*methoxyphenyl*)*prop*-1-*ynyl*]-3′,5′-*di*-O-(*p*-*toluoyl*)-2′-*deoxyuridine* **23**. This was synthesized according to the procedure for compound **22** by utilising 1-(*p*-methoxyphenyl)prop-2-yn-1-ol (160 mg, 0.98 mmol) in 88% yield, which was crystallised from chloroform–diethyl ether, to give *compound* **23**, m.p. 222–224 °C (Found: C, 67.3; H, 5.3; N, 4.7. $C_{35}H_{32}N_2O_9$ requires C, 67.30; H, 5.2; N, 4.5%); ν_{max}/cm^{-1} 3450 br, 1710, 1670 and 1610; λ_{max}/nm 284 (ε 18 200) and 237 (54 950); δ($CDCl_3$; 100 MHz) 2.08–2.96 (2 H, m, 2′-H_2), 2.32 (3 H, s, Ar*Me*), 2.40 (3 H, s, Ar*Me*), 3.76 (3 H, s, ArO*Me*), 4.40–4.88 (3 H, m, 4′-H and 5′-H_2), 5.36–5.68 (2 H, m, 3′- and C*H*OH), 6.24–6.48 (1 H, dd, 1′-H), 6.72–8.16 (13 H, m, ArH and 6-H) and 8.60 (1 H, br s, NH).

5-[3-*Hydroxy*-3-(o-*tolyl*)*prop*-1-*ynyl*]-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridine* **24**. This was prepared in 83% yield from 1-(*o*-tolyl)prop-2-yn-1-ol (150 mg, 1.02 mmol) and the other reagents as for compound **22**; after purification by chromatography, a foam was obtained; this was crystallised from chloroform–diethyl ether to give *compound* **24**, m.p. 216–218 °C (Found: C, 68.7; H, 5.1; N, 4.6. $C_{35}H_{32}N_2O_8$ requires C, 69.1; H, 5.30; N, 4.60%); ν_{max}/cm^{-1} 3440 br, 1720, 1710, 1670 and 1610; λ_{max}/nm 291 (ε 12 880) and 239 (38 020); δ($CDCl_3$; 200 MHz) 2.22–2.96 (2 H, m, 2′-H_2), 2.40 (3 H, s, Ar*Me*), 2.42 (3 H, s, *ArMe*), 2.46 (3 H, s, Ar*Me*), 4.58–4.86 (3 H, m, 4′-H and 5′-H_2). 5.58–5.74 (2 H, m, 3′- and C*H*OH), 6.36–6.46 (1 H, dd, 1′-H), 7.18–7.40 (7 H, m, ArH), 7.64–7.74 (1 H, m, ArH_o), 7.88–8.04 (5 H, m, ArH and 6-H) and 8.94 (1 H, br s, NH).

5-(*Acylethynyl*)-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridines* **25**–**28**.—*Method A. PCC oxidation of* 5-(3-*aryl*-3-*hydroxyprop*-1-*ynyl*)-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridines. General procedure*. To a magnetically stirred solution of 5-(3-hydroxy-3-phenylprop-1-ynyl)-3′,5′-di-*O*-(*p*-toluoyl)-2′-deoxyuridine **21** (100 mg, 0.17 mmol) in dichloromethane (25 cm^3) was added PCC (340 mg, 1.58 mmol). The mixture was stirred at room temperature for 2 h, filtered, and the residue was washed with dichloromethane (3 × 10 cm^3). The combined filtrates, on evaporation of solvent, furnished a solid, which was purified on a short column of silica gel (60–120 mesh; 10% ethyl acetate in chloroform as eluent) to yield 5-(*benzoylethynyl*)-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridine* **25** as a solid (90 mg, 90%), which was crystallised from methanol, m.p. 220 °C (Found: C, 68.7; H, 4.9; N, 4.7. $C_{34}H_{28}N_2O_8$ requires C, 68.9; H, 4.8; N, 4.7%); ν_{max}/cm^{-1} 2200 s, 1730, 1715, 1695, 1640, 1620, 1610 and 1595; λ_{max}/nm 325.6 (ε 22 390) and 243 (39 810); δ($CDCl_3$; 100 MHz) 2.08–2.96 (2 H, m, 2′-H_2), 2.24 (3 H, s, Ar*Me*), 2.40 (3 H, s, Ar*Me*), 4.40–4.96 (3 H, m, 4′-H and 5′-H_2), 5.44–5.76 (1 H, apparent doublet, 3′-H), 6.16–6.48 (1 H, dd, 1′-H), 7.04–8.48 (14 H, m, ArH and 6-H) and 8.96 (1 H, br s, NH).

3′,5′-*Di*-O-(p-*toluoyl*)-5-(p-*toluoylethynyl*)-2′-*deoxyuridine* **26**. This *compound* was obtained in 90% yield, and was crystallised from methanol, m.p. 222 °C (Found: C, 69.6; H, 5.4; N, 4.45. $C_{35}H_{30}N_2O_8$ requires C, 69.3; H, 5.0; N, 4.6%); ν_{max}/cm^{-1} 2200 s, 1730, 1720, 1695, 1635 and 1605; λ_{max}/nm 326 (ε 24 000) and 241 (37 150); δ($CDCl_3$; 270 MHz) 2.26 (1 H, m, 2′-H), 2.28 (3 H, s, Ar*Me*), 2.44 (6 H, s, Ar*Me*), 2.84 (1 H, m, 2′-H), 4.60–4.86 (3 H, m, 4′-H and 5′-H_2), 5.56 (1 H, m, 3′-H), 6.34 (1 H, dd, *J* 5.37 and 8.42, 1′-H), 7.17–8.15 (12 H, m, ArH), 8.20 (1 H, s, 6-H) and 8.37 (1 H, s, NH).

5-(p-*Methoxybenzoylethynyl*)-3′,5′-*di*-O-(p-*toluoyl*)-2′-*deoxyuridine* **27**. This *compound* was prepared in 90% yield, and was crystallised from methanol, m.p. 212–214 °C (Found: C, 67.3; H, 5.0; N, 4.8. $C_{35}H_{30}N_2O_9$ requires C, 67.5; H, 4.9; N, 4.50%); ν_{max}/cm^{-1} 2210, 1730, 1720, 1700, 1635, 1615 and 1600; λ_{max}/nm 332.5 (ε 38 900) and 242 (56 230); δ($CDCl_3$; 100 MHz) 2.16–2.96 (2 H, m, 2′-H_2), 2.24 (3 H, s, Ar*Me*), 2.40 (3 H, s, Ar*Me*), 3.84 (3 H, s, ArO*Me*), 4.48–4.88 (3 H, m, 4′-H and 5′-H_2), 5.44–5.76 (1 H, apparent d, 3′-H), 6.16–6.48 (1 H, dd, 1′-H), 6.88–8.32 (13 H, m, ArH and 6-H) and 8.72 (1 H, s, NH).

3′,5′-*Di*-O-(p-*toluoyl*)-5-(o-*toluoylethynyl*)-2′-*deoxyuridine* **28**. This *compound* was also obtained in 90% yield, from PCC oxidation of the alcohol **24** and was crystallised from methanol, m.p. 223–224 °C (Found: C, 69.6; H, 4.7; N. 4.7. $C_{35}H_{30}N_2O_8$ requires C, 69.3; H, 5.0; N, 4.6%; ν_{max}/cm^{-1} 2200 s, 1730, 1715, 1695, 1640, 1620 and 1610; λ_{max}/nm 323 (ε 28 180) and 242

(47 860); δ($CDCl_3$, 100 MHz) 2.08–2.96 (2 H, m, 2'-H_2), 2.24 (3 H, s, Ar*Me*), 2.40 (3 H, s, Ar*Me*), 2.60 (3 H, s, Ar*Me*), 4.48–4.96 (3 H, m, 4'-H and 5'-H_2) 5.52–5.76 (1 H, apparent d, 3'-H), 6.24–6.48 (1 H, dd, 1'-H), 7.12–8.40 (13 H, m, ArH and 6-H) and 8.80 (1 H, br s, NH).

Method B. Palladium-mediated synthesis of 5-(*acylethynyl*)-3',5'-*di*-O-(p-*toluoyl*)-2'-*deoxyuridines. Typical procedure. Synthesis of* 5-(*benzoylethynyl*)-3',5',-*di*-O-(p-*toluoyl*)-2'-*deoxyuridine* **25**. To a well stirred solution of 5-iodo-3',5'-di-*O*-(*p*-toluoyl)-2'-deoxyuridine **20** (280 mg, 0.47 mmol) in acetonitrile (10 cm^3) under nitrogen were added bis(triphenylphosphine)palladium(II) chloride (40 mg, 0.057 mmol), copper(I) iodide (20 mg, 0.10 mmol) and, after 15 min, 1-phenylprop-2-yn-1-one (130 mg, 1 mmol). The mixture was stirred for 1 h and then sodium hydrogen carbonate (100 mg, 1.2 mmol) was added. This mixture was further heated at 50 °C for 8 h and then the solvent was removed to yield a black residue, which was purified by chromatography (SiO_2, 60–120 mesh; 10% ethyl acetate in chloroform as eluent) to give compound **25** as a solid (50 mg, 17.80%), which was crystallised from methanol, m.p. 218 °C, identical with the sample synthesized by Method A (from spectroscopic comparisons).

5-(p-*Methoxybenzoylethynyl*)-3',5'-*di*-O-(p-*toluoyl*)-2'-*deoxyuridine* **27**. This compound was synthesized from compound **20** (280 mg, 0.47 mmol), 1-(*p*-methoxyphenyl) prop-2-yn-1-one (160 mg, 1 mmol) and the other reagents as under compound **25** according to Method B. After purification by column chromatography, solid compound **27** (60 mg, 20%) was obtained, which was crystallised from methanol, m.p. 212 °C, identical with the sample synthesized by Method A [from spectroscopic (IR, UV and ^1H NMR) comparisons].

5-(*Acylethynyl*)-2'-*deoxyuridines* **29–32**.—*Typical procedure. Synthesis of* 5-(*benzoylethynyl*)-2'-*deoxyuridine* **29**. A mixture of 5-(benzoylethynyl)-3',5'-di-*O*-(*p*-toluoyl)-2'-deoxyuridine **25** (50 mg, 0.08 mmol) and sodium methoxide [made from sodium (4.14 mg, 0.18 mmol) and anhydrous methanol (4 cm^3)] was stirred at room temperature for 6 h, when TLC indicated complete conversion of the starting material. The solution was carefully neutralised by addition of Dowex 50–X8 (H^+) resin, filtered, and the resin was washed with methanol. The combined filtrates, on evaporation, gave a solid, which was triturated with diethyl ether three times to remove the ester formed. The resultant *solid* (25 mg, 83%) was crystallised from ethanol–light petroleum (60–80 °C; a few drops) and had m.p. 184–185 °C (Found: C, 60.5; H, 4.2; N, 8.1. $C_{18}H_{16}N_2O_6$ requires C, 60.7; H, 4.5; N, 7.9%); ν_{max}/cm^{-1} 2200, 1730, 1685 and 1610; λ_{max}/nm 330 (ε 20 890); δ([$^2H_6$]DMSO; 100 MHz) 2.18 (2 H, m, 2'-H_2), 3.68 (2 H, m, 5'-H_2), 3.84 (1 H, br s, 4'-H), 4.24 (1 H, m, 3'-H), 5.28 (2 H, m, 2 × OH), 6.12 (1 H, t, 1'-H), 7.36–8.00 (3 H, m, $ArH_{m,p}$), 8.08–8.40 (2 H, m, ArH_o), 8.80 (1 H, s, 6-H) and 11.92 (1 H, br s, NH).

5-(p-*Toluoylethynyl*)-2'-*deoxyuridine* **30**. This compound was obtained from 5-(*p*-toluoylethynyl)-3',5'-di-*O*-(*p*-toluoyl)-2'-deoxyuridine **26** by following the above procedure, in 82% yield; and was crystallised from ethanol–light petroleum (60–80 °C), m.p. 188–190 °C (Found: C, 62.0; H, 4.6; N, 7.5. $C_{19}H_{18}N_2O_6$ requires C, 61.6; H, 4.90; N, 7.6%); ν_{max}/cm^{-1} 2210, 1700, 1680, 1640, 1615 and 1600; λ_{max}/nm 330 nm (ε 25 120); δ([$^2H_6$]DMSO; 200 MHz) 2.25 (2 H, m, 2'-H_2), 2.45 (3 H, s, Ar*Me*), 3.70 (2 H, m, 5'-H_2), 3.90 (1 H, m, 4'-H), 4.30 (1 H, m, 3'-H), 5.32 (2 H, m, 2 × OH), 6.12 (1 H, t, 1'-H), 7.46 (2 H, d, *J* 10.0, ArH_m), 8.12 (2 H, d, *J* 10, ArH_o), 8.20 (1 H, s, 6-H) and 11.92 (1 H, br s, NH).

5-(p-*Methoxybenzoylethynyl*)-2'-*deoxyuridine* **31**. This *compound* was prepared in 80% yield and had m.p. 205 °C (Found: C, 59.1; H, 5.0; N, 7.0. $C_{19}H_{18}N_2O_7$ requires C, 59.1; H, 4.7; N, 7.25%); ν_{max}/cm^{-1} 2210, 1700, 1670, 1630, 1615 and 1600; λ_{max}/nm 335 (ε 33 110); δ([$^2H_6$]DMSO: 100 MHz) 2.24 (2 H, apparent tr, 2'-H_2), 3.68 (2 H, m, 5'-H_2), 3.84 (4 H, s, ArO*Me* and 4'-H), 4.32 (1 H, m, 3'-H), 5.28 (2 H, m, 2 × OH), 6.12 (1 H, t, 1'-H), 7.12 (2 H, d, *J* 10.0, ArH_m), 8.16 (2 H, d, *J* 10.0, ArH_o), 8.72 (1 H, s, 6-H) and 11.92 (1 H, s, NH).

5-(o-*Toluoylethynyl*)-2'-*deoxyuridine* **32**. This *compound* was synthesized from 3',5'-di-*O*-(*p*-toluoyl)-5-(*o*-toluoylethynyl)-2'-deoxyuridine **28** in 82% yield, and had m.p. 167–168 °C (Found: C, 61.5; H, 4.8; N, 7.7. $C_{19}H_{18}N_2O_6$ requires C, 61.6; H, 4.90; N, 7.6%); ν_{max}/cm^{-1} 2210, 1710, 1690, 1630 and 1610; λ_{max}/nm 325 (ε 21 380); δ([$^2H_6$]DMSO; 100 MHz) 2.20 (2 H, t, 2'-H_2), 2.56 (3 H, s, Ar*Me*), 3.60 (2 H, m, 5'-H_2), 3.84 (1 H, m, 4'-H), 4.24 (1 H, m, 3'-H), 5.20 (2 H, m, 2 × OH), 6.12 (1 H, t, 1'-H), 7.28–7.68 (3 H, m, $ArH_{m,p}$), 8.24–8.40 (1 H, m, ArH_o), 8.72 (1 H, s, 6-H) and 11.84 (1 H, s, NH).

Acknowledgements

Financial assistance from the Department of Science and Technology, Government of India, under a grant to N. G. K. (Grant No. SP/S1/G-45/88) is gratefully acknowledged. Thanks are due to Dr. D. F. Ewing, University of Hull, for the 270 MHz NMR spectra. We also thank Dr. C. P. Spears of the University of Southern California, Comprehensive Cancer Center, Los Angeles, California, USA, for samples of 5-iodo-2'-deoxyuridine.

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Paper 3/01865B
Received 1*st April* 1993
Accepted 14*th July* 1993