Synthesis of Analogues of 5-Iodo-2'-deoxyuridine-5'-diphosphate

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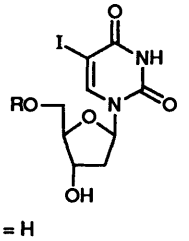
The synthesis of three types of diphosphate analogues of 5-iodo-2'-deoxyuridine-5'-diphosphate is reported. Routes are described to the 5'-phosphonoacetamido, the 5'-*N*-phosphonosulfamoyl and the 5'-*O*-sulfamoylcarbamoyl derivatives, **2**, **3** and **4** starting from 5-iodo-2'-deoxyuridine (IDU). In the course of the synthesis of **3**, the 5'-sulfamoyl derivative **19**, an analogue of IDU 5'-monophosphate was prepared. The antiherpes virus activity of **2**, **4** and **19** is reported.

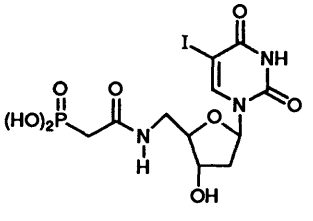
The design of selective inhibitors of virally specified enzymes has been the subject of considerable research effort in recent years.[1] In the case of the herpes viruses, a number of nucleoside analogues have now been shown to be selective inhibitors of viral DNA polymerases. These include the 5-substituted 2'-deoxyuridines[2] such as (*E*)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU),[3] and acyclonucleosides[4,5] such as acyclovir (ACV).[6–8] Similarly, for human immunodeficiency virus (HIV) the aetiologic agent in AIDS, the dideoxynucleoside series of compounds represent a group of selective inhibitors of the virally encoded RNA-dependant DNA polymerase, reverse transcriptase.[9–11] In all cases, these nucleoside analogues act as polymerase inhibitors after transformation to their triphosphates in a sequence of steps carried out by viral or cellular enzymes. It has been suggested that their potency is dependant on the efficiency by which they are converted into triphosphates in infected cells.[12]

The importance of finding metabolically stable analogues of mono, di-and tri-phosphates of nucleosides and acyclonucleosides has also been recognised.[13–21] Such analogues may be able to bypass some of the phosphorylation steps required to produce the nucleosides in their active triphosphate forms. Additionally, they could be active *per se* against other virally specified enzymes, such as the HSV-1 encoded enzyme ribonucleotide reductase,[22] which catalyses the reduction of all four ribonucleoside 5'-diphosphates.

In our recent research, we have been attempting to identify mimics of the diphosphate group, and have recently reported on the preparation and antiviral activity of a series of diphosphonate derivatives of pyrimidine and purine acyclonucleosides.[23] We have subsequently been studying other potential bioisosteric replacements for the diphosphate moiety. In this publication, we describe synthetic routes to three types of diphosphate analogues of the commercially available antiherpes agent 5-iodo-2'-deoxyuridine **1** (IDU), namely the 5'-phosphonoacetamido derivative **2**, the 5'-*N*-phosphonosulfamoyl derivative **3**, and the 5'-*O*-sulfamoylcarbamoyl derivative **4**.[24]



1 R = H
3 R = $(HO)_2P(O)NHSO_2$—
4 R = $H_2NSO_2NHC(O)$—



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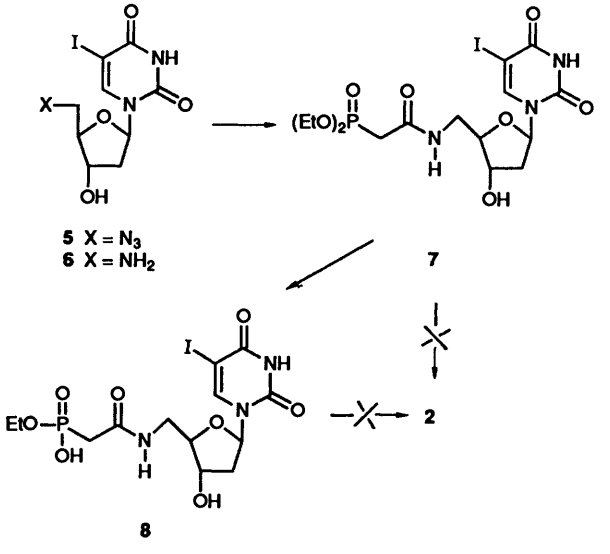
Results and Discussion

Synthesis of the 5'-Acetamido Derivative of IDU.—Phosphonoacetic acid (PAA) is a known antiherpes virus agent which can act as a mimic of pyrophosphate, and, by interfering with its binding site on viral DNA, can inhibit viral DNA polymerase.[25] Phosphonoacetic acid derivatives of modified nucleosides have been prepared, but as these are metabolically susceptible to cleavage by cellular esterases, any antiviral activity demonstrated has been attributed to that of the component molecules.[26] We chose therefore to synthesise the more stable phosphonoacetamido derivative of IDU, **2**.

We envisaged that a facile synthesis of the phosphonoacetamido derivative **2** would be possible by coupling 5'-amino-5-iodo-2',5'-dideoxyuridine **6** with diethyl phosphonoacetic acid to give **7**, followed by deesterification (Scheme 1).



5 X = N_3
6 X = NH_2
7
8
2

Scheme 1

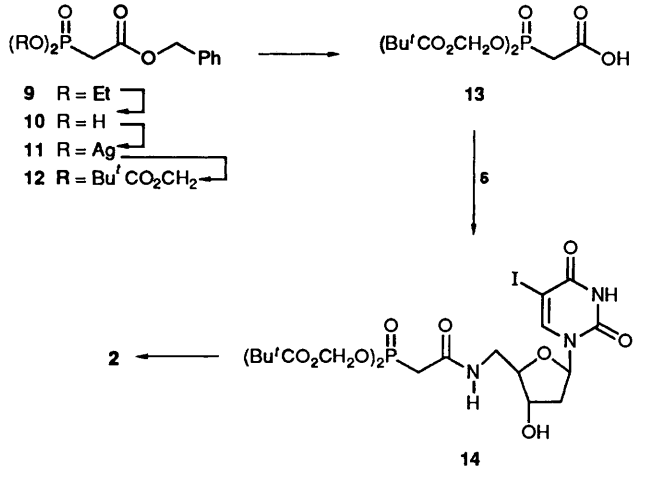
5'-Amino-5-iodo-2',5'-dideoxyuridine was prepared from IDU by the literature procedure.[27,28] The final stage in the synthesis of **6** required reduction of 5'-azido-5-iodo-2',5'-dideoxyuridine **5**, using triphenylphosphine in pyridine followed by hydrolysis with aqueous ammonia. In our hands, yields of the amine **6** were poor using this method. However, the yield of **6** was substantially improved by reduction of **5** with triphenylphosphine in tetrahydrofuran (THF) followed by aqueous hydrolysis.[29]

Reaction of **6** with diethylphosphonoacetic acid[30] in the presence of dicyclohexylcarbodiimide[31] gave a 73% yield of the coupled product **7**. However, attempted deprotection of the

diester using the standard conditions of bromotrimethylsilane in anhydrous acetonitrile failed to yield the required phosphonic acid **2**. Instead a complex mixture of products resulted, from which evidence was obtained of loss of iodine from the heterocyclic base. A similar result was obtained using chlorotrimethylsilane in the presence of sodium iodide.[32]. Alternative methods of deprotection were therefore investigated.

On treatment of **7** with toluene-4-sulfonic acid in *N,N*-dimethylformamide (DMF),[33] no reaction occurred. Under stronger acid conditions, decomposition was evident. Partial deprotection of the diester function was achieved by treatment with aqueous sodium hydroxide (1 mol dm^{-3}) in dioxane giving the monoester **8**. Attempted deesterification of **8** using the phosphodiesterases[34] from *crotalus durissus* and *crotalus adamanteus*, incubating in a solution of Tris HCl at pH 8.5 at 37 °C for 18 h, resulted only in recovery of starting material.

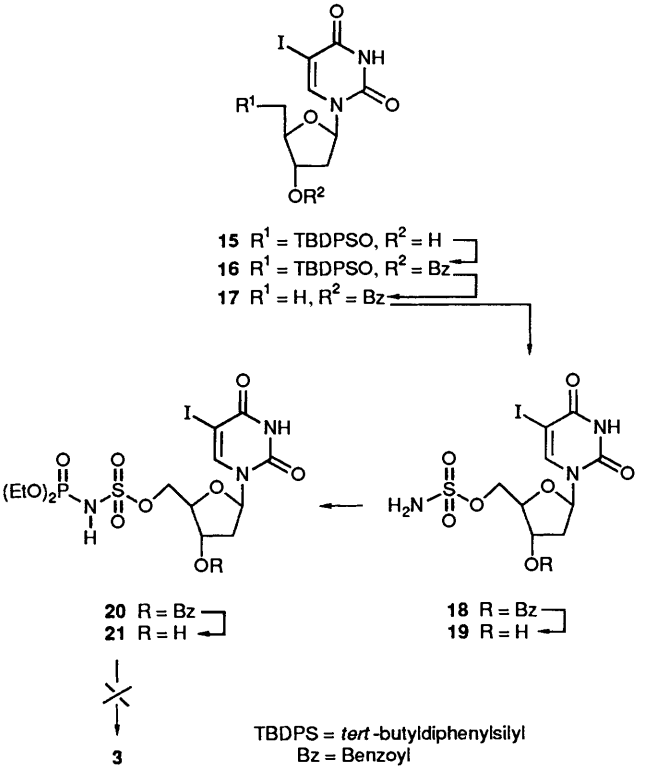
Since it proved impossible to deprotect the diethyl ester function of **7** in the presence of the iodo substituent on the heterocyclic ring, an alternative protecting group for the phosphonic acid was sought, for which mild deprotection conditions, avoiding the use of bromotrimethylsilane, could be employed. Recently, Iyer *et al.*[35] have reported on the preparation of a series of acyloxyalkyl esters of phosphonoformic acid (foscarnet) for evaluation as hydrolysable prodrugs of foscarnet. We applied their synthetic methodology to the preparation of the dipivaloyloxymethyl ester of phosphonoacetic acid **13** (Scheme 2).



Scheme 2

Reaction of diethylphosphonoacetic acid with benzyl bromide gave the benzyl ester **9** in 70% yield. Treatment of **9** with bromotrimethylsilane gave the phosphonic acid **10** in 84% yield, and this was converted into the dipivaloyloxymethyl derivative **12** in 51% yield by means of the light sensitive disilver salt **11**. The benzyl ester group was removed by hydrogenolysis over palladium–charcoal catalyst under neutral conditions to afford the acid **13** in 97% yield. Condensation of **13** with 5′-amino-5-iodo-2′,5′-dideoxyuridine **6** was achieved using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in the presence of *N*-hydroxybenzotriazole, affording the dipivaloyloxymethyl ester **14** in 93% yield. Finally the bis-pivaloyloxymethyl group was successfully removed to give the phosphonic acid **2** by treatment with methanolic hydrochloric acid either at room temperature (55% after 48 h reaction time) or at 45 °C (70% after 7 h reaction time).

Synthesis of the 5′-N-Phosphonosulfamoyl and 5′-O-(Sulfamoylcarbamoyl Derivatives of IDU.—The sulfamoyl group present in **3** is a feature of the naturally occurring antibiotic nucleoside analogue nucleocidin, in which it is believed to represent a bioisosteric replacement for a monophosphate group.[36] The *O*-sulfamoylcarbamoyl group present in **4** has been reported to be a bioisosteric replacement for the diphosphate linkage in a series of uridine 5′-glucose diphosphate analogues, which are reported to exhibit antiviral activity by inhibition of glycosylating proteins.[37,38] The synthesis of analogues **3** and **4** required the preparation of a common 3′-protected intermediate of IDU (Scheme 3). During the course of the synthesis of **3**,



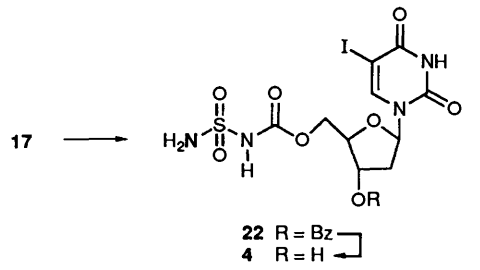
Scheme 3

the 5′-sulfamoyl derivative **19** an analogue of IDU 5′-monophosphate was prepared for biological evaluation.

The 5′-*tert*-butyldiphenylsilyl derivative of IDU, **15**, was prepared, by reaction of IDU with *tert*-butylchlorodiphenylsilane in the presence of imidazole.[39] This was converted into the 3′-benzoate **16** in 80% yield by reaction with benzoic anhydride in pyridine at room temperature in the presence of 4-*N,N*-dimethylaminopyridine (DMAP). (In the absence of DMAP no acylation occurred). The *tert*-butyldiphenylsilyl protecting group was removed using methanolic hydrogen chloride at room temperature to give the required intermediate **17** in 92% yield.

Treatment of **17** with three equivalents of sodium hydride, followed by reaction with sulfamoyl chloride[40] afforded the 5′-sulfamoyl derivative **18** in 56% yield.[41] A sample of this material was deprotected by treatment with sodium methoxide in methanol giving **19** in 60% yield. Further reaction of **18** with sodium hydride followed by treatment with diethyl chlorophosphate gave the 5′-diethyl-*N*-phosphonosulfamoyl derivative **20** in 51% yield, and this was also deprotected to yield **21** using sodium methoxide in methanol. Unfortunately, problems were again encountered in the deesterification of **21** using bromotrimethylsilane, and it was not possible to progress this compound through to compound **3**. However, the synthetic methodology developed here is applicable to the synthesis of other nucleoside derivatives of this type.

Reaction of the 3′-benzoate **17** with chlorosulfonylisocyanate at −20 °C, followed by treatment with ammonia,[38] gave the *O*-sulfamoylcarbamoyl derivative **22** in 76% yield (Scheme 4) and



Scheme 4

this was deprotected without problems using sodium methoxide in methanol to give **4** in 53% yield.

Compounds **2**, **4** and **19** were screened against viruses of the herpes family, including herpes simplex virus types 1 and 2, varicella zoster virus and human cytomegalovirus. Compound **2** was inactive in all screens, and compounds **4** and **19** showed activity against herpes simplex virus type 1 at 30 and 20 μg cm^3, respectively.

Experimental

IR spectra were recorded on a Perkin-Elmer 580 or Bio-Rad FTS spectrometer; UV spectra were obtained on a Cary 219 spectrometer. NMR spectra were obtained on JEOL GX270 and Bruker AM 400 spectrometers, *J* values are given in Hz. Mass spectroscopy was performed using a JEOL SX-102 instrument operating at 70 eV. M.p.s were determined using a Reichert-Koffler apparatus and are uncorrected. Elemental analysis was carried out on a CC440 Elemental Analyser.* Organic solutions of products were dried using magnesium sulfate and chromatography was performed on Merck 7736 60H silica gel. All compounds were homogeneous by TLC on silica gel $60F_{254}$ coated aluminium sheets. The preparation of compound **12** was carried out using degassed solvents, under an argon atmosphere in the absence of light.

5'-Amino-5-iodo-2',5'-dideoxyuridine **6**.—A solution of 5'-azido-5-iodo-2',5'-dideoxyuridine **5** (2.5 g, 6.6 mmol) in anhydrous tetrahydrofuran (THF) (75 cm^3) was treated with triphenylphosphine (2.94 g, 11.22 mmol). The mixture was stirred at room temperature for 24 h, then treated with water (178 mm^3, 9.9 mmol). After stirring at room temperature for an additional 24 h, water (50 mm^3) was added, and, after additional stirring at room temperature for 48 h, the solvent was evaporated under reduced pressure. The residue was dissolved in a 1% solution of methanolic hydrogen chloride (150 cm^3) and the solvent was evaporated under reduced pressure. The residue was partitioned between water (150 cm^3) and ethyl acetate (150 cm^3) and the aqueous phase reduced in volume to approximately 40 cm^3 under reduced pressure. This solution of the hydrochloride of **6** was applied to a chromatography column of reverse phase C_{18} silica gel, and the hydrochloride was purified eluting with water. The resulting aqueous solution of the hydrochloride of **6** was evaporated under reduced pressure to 100 cm^3, and was treated with a solution of ammonium hydroxide (1 mol dm^{-3}), to pH11. On concentration of the solution, by evaporation under reduced pressure, to 40 cm^3, compound **6** precipitated out as a white crystalline solid (800 mg). This procedure of addition of ammonium hydroxide solution and evaporation of the solvent was repeated another three times to yield a total of 1.45 g of **6** as a white solid (62%), m.p. 201–202 °C, decomp.; ν_{max}(KBr)/cm^{-1} 3422, 3071, 2276, 1642, 1605, 1512 and 1441; δ_H[$(CD_3)_2SO$] 1.95–2.3 (2 H, m, 2'-CH_2), 2.7–2.82 (2 H, m, 5'-CH_2), 3.57–3.77 (1 H, m, 4'-CH), 4.07–4.3 (1 H, m, 3'-CH), 4.0–6.0 (3 H, br s, 3 × D_2O exchangeable NH), 5.07–5.2 (1 H, m, D_2O exchangeable 3'-OH), 5.95–6.2 (1 H, m, 1'-CH) and 8.42 (1 H, s, 6-H) (Found: C, 30.4; H, 3.4; N, 11.65. $C_9H_{12}IN_3O_4$ requires C, 30.6; H, 3.4; N, 11.9%).

5'-Diethoxyphosphorylacetamido-5-iodo-2',5'-dideoxyuridine **7**.—A mixture of compound **6** (0.5 g, 1.4 mmol) and diethoxyphosphorylacetic acid (0.28 g, 1.4 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (40 cm^3), was treated dropwise with a solution of dicyclohexylcarbodiimide (0.322 g, 1.27 mmol) in anhydrous DMF (8 cm^3). The resulting mixture was stirred at room temperature for 5 h, and treated with acetic anhydride (50 mg). After stirring for a further 30 min, the white precipitate was filtered off, the filtrate was evaporated under reduced pressure and the residue was purified by chromatography on silica gel eluting with chloroform–methanol (95:5) to give the *title compound* **7** as a white solid (0.55 g, 73%); m.p. 87–90 °C decomp.; ν_{max}(KBr)/cm^{-1} 3405, 3376, 3062, 2985, 2931, 2855, 2818, 1699, 1608, 1553 and 1446; δ_H[$(CD_3)_2SO$] 1.1–1.37 (6 H, t, *J* 6.5, 2 × CH_3), 1.9–2.4 (2 H, m, 2'–CH_2), 2.75–3.05 (2 H, d, *J* 22, CH_2P), 3.15–3.5 (2 H, m, 5'-CH_2), 3.65–3.8 (1 H, m, 4'-CH), 3.87–4.27 (5 H, m, 3'-CH, 2 × CH_2), 5.27 (1 H, d, *J* 4.4, D_2O exchangeable 3'-OH), 5.95–6.15 (1 H, m, 1'-CH), 8.05 (1 H, s, 6-H), 8.1–8.25 (1 H, s, D_2O exchangeable 5'-NH) and 11.6 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 33.8; H, 4.25; N, 7.6. $C_{15}H_{23}IN_3O_8P$ requires C, 33.9; H, 4.3, N, 7.9%).

5'-Ethoxy(hydroxy)phosphorylacetamido-5-iodo-2',5'-dideoxyuridine **8**.—A solution of compound **7** (0.3 g. 0.57 mmol) in dioxane (15 cm^3) was treated with sodium hydroxide solution (1 mol dm^{-3}; 1.13 cm^3, 1.13 mmol) and the mixture was stirred at room temperature for 1 h. Additional sodium hydroxide solution (1.7 cm^3, 1.7 mmol) was added and the solution was stirred at room temperature for 12 h. After neutralisation of the mixture with Amberlite IR 120H ion exchange resin and filtration, the solvent was evaporated under reduced pressure and the residue was purified by chromatography on C_{18} reverse phase silica gel eluting with water to give the *title compound* **8** as a white solid (0.24 g, 85%), m.p. 190–192 °C, decomp.; ν_{max}(KBr)/cm^{-1} 3285, 3088, 2977, 1699, 1639, 1654, 1479, 1426 and 1409; δ_H[$(CD_3)_2SO$] 1.12 (3 H, t, *J* 7, CH_3), 1.9–2.4 (2 H, m, 2'-CH_2), 2.3–2.7 (2 H, m, CH_2P), 3.0–4.0 (1 H, br s, D_2O exchangeable HOP), 3.2–3.5 (1 H, m, 5'-CH_2), 3.6–4.0 (3 H, m, CH_2, 4'-CH), 4.07–4.25 (1 H, m, 3'-CH), 6.02 (1 H, m, 1'-CH), 8.12 (1 H, s, 6-H), 8.27 (1 H, s, D_2O exchangeable 5'-NH) and 11.69 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 30.1; H, 3.6; N, 8.2. $C_{13}H_{19}IN_3O_8P$·0.6 H_2O requires C, 30.4; H, 3.9; N, 8.2%).

Benzyl Diethoxyphosphorylacetate **9**.—A solution of diethoxyphosphorylacetic acid (2 g, 10.2 mmol) diisopropylethylamine (1.78 cm^3, 10.2 mmol) and 4-*N*,*N*-dimethylaminopyridine (50 mg), in anhydrous acetonitrile (20 cm^3) was treated dropwise with benzyl bromide (1.22 cm^3, 10.2 mmol) and the mixture was stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure and the residue was treated with diethyl ether (50 cm^3). After filtration of the white precipitate, the filtrate was evaporated under reduced pressure and the residue was purified by chromatography on silica gel eluting with ethyl acetate–hexane (9:1) to give the *title compound* **9** as an oil (2.05 g, 70%); ν_{max}(KBr)/cm-^{1} 3428, 2983, 2908, 2873, 1736 and 1456; δ_H($CDCl_3$) 1.29 (6 H, t, *J* 7.1, 2 × CH_3), 3.01 (2 H, d, *J* 21, CH_2P), 4.02–4.25 (4 H, m, 2 × CH_2), 5.18 (2 H, s, CH_2O) and 7.25–7.42 (5 H, m, C_6H_5)

* It was often necessary to incorporate particle moles of water in the analytical data for the compounds described here because of their hygroscopic nature and the difficulties in preparing completely anhydrous samples.

(Found: C, 54.05; H, 6.9. $C_{13}H_{19}O_5P \cdot 0.2H_2O$ requires C, 53.9; H, 6.75%).

Benzyl Phosphonoacetate **10**.—A solution of compound **9** (1.4 g, 4.89 mmol) in anhydrous acetonitrile (15 cm^3) was treated with bromotrimethylsilane (1.94 cm^3, 14.67 mmol) under nitrogen and the mixture was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on reverse phase C_{18} silica gel eluting with water to give the *title compound* **10** as an oil (944 mg, 84%); ν_{max}(KBr)/cm^{-1} 3398, 3038, 2937, 2359, 2334, 2271, 1730, 1498 and 1404; δ_H($CDCl_3$) 3.0 (2 H, d, *J* 21, CH_2P), 5.15 (2 H, s, CH_2O), 7.12–7.5 (5 H, m, C_6H_5) and 9.9 (2 H, s, 2 × D_2O exchangeable OH) (Found: C, 44.3; H, 4.9. $C_9H_{11}O_5P \cdot 0.7H_2O$ requires C, 44.5; H, 5.15%).

Benzyl Bis(pivaloyloxymethoxy)phosphorylacetate **12**.—A solution of compound **10** (8.1 g, 35.2 mmol) in methanol (60 cm^3) at 0–5 °C under argon in the absence of light was treated dropwise with a solution of silver nitrate (11.96 g, 70.41 mmol) in methanol–water 75:25 (168 cm^3). After stirring at 0–5 °C for 15 min, the precipitated white silver salt of **12** was filtered under an atmosphere of argon in the absence of light and was dried by evacuation (0.5 mmHg) for 1 h, at 5 °C.

The resulting solid was suspended in anhydrous toluene (25 cm^3) at −78 °C and treated dropwise with freshly distilled iodomethyl pivaloate (18 g, 74.39 mmol) over a period of 30 min. The resulting mixture was stirred at −78 °C for 4 h, warmed to room temperature and stirred for 18 h. The resulting red mixture was filtered and the yellow precipitate of silver iodide was washed with toluene (20 cm^3). The combined toluene solutions were extracted with a cooled 5% aqueous solution of sodium thiosulfate (2 × 100 cm^3), then washed with cold water (100 cm^3). The organic phase was dried and evaporated under reduced pressure and the residue was purified by chromatography on silica gel eluting with ethyl acetate–hexane (1:3) to give the *title compound* **12** as an oil (8.12 g, 51%); ν_{max}(KBr)/cm^{-1} 3452, 2975, 2934, 2874, 1752, 1497, 1481, 1458 and 1396; δ_H($CDCl_3$) 1.22 [18 H, s, 2 × $(CH_3)_3C$], 3.22 (2 H, d, *J* 21, CH_2P), 5.17 (2 H, s, OCH_2Ph), 5.62 (4 H, d, *J* 13.2, 2 × OCH_2O) and 7.36 (5 H, m, C_6H_5) (Found: C, 54.8; H, 7.1. $C_{21}H_{31}O_9P$ requires C, 55.0; H, 6.8%).

Bis(pivaloyloxymethoxy)phosphorylacetic Acid **13**.—A solution of compound **12** (1 g, 2.18 mmol) in anhydrous THF (45 cm^3) was treated with 10% palladium–charcoal catalyst (1.16 g, 1.09 mmol). The mixture was hydrogenated at atmospheric pressure and room temperature for 3.5 h, filtered through a glass fibre pad and the solvent was evaporated under reduced pressure to give the *title compound* **13** as an oil (780 mg, 97%). An analytically pure sample was obtained by chromatography on silica gel, eluting with ethyl acetate–hexane (1:1); ν_{max}(KBr)/cm^{-1} 3444, 2977, 2937, 2876, 2642, 2536, 1755, 1462, 1428, 1412 and 1400; δ_H($CDCl_3$) 1.23 [18 H, s, 2 × $(CH_3)_3C$], 3.12 (2 H, d, *J* 22, CH_2P), 5.75 (4 H, d, *J* 13.3, 2 × OCH_2O) and 7–7.5 (1 H, br s, D_2O exchangeable CO_2H) (Found: C, 45.0; H, 7.0. $C_{14}H_{25}O_9P \cdot 0.25\ H_2O$ requires C, 45.1; H, 6.8%).

5′-Bis(pivaloyloxymethoxy)phosphorylacetamido-5-iodo-2′,5′-dideoxyuridine **14**.—A solution of 5′-amino-5-iodo-2′,5′-dideoxyuridine (200 mg, 0.57 mmol), compound **13** (230 mg, 0.62 mmol) and *N*-hydroxybenzotriazole (115 mg, 1.85 mmol) in anhydrous DMF (25 cm^3) was treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (130 mg, 0.68 mmol). The mixture was stirred at room temperature for 3 h, and the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel eluting with chloroform–methanol (9:1) to give the *title compound* **14** as a white solid, m.p. 80 °C decomp., (0.37 g, 93%); ν_{max}(KBr)/cm^{-1} 3400, 3059, 2975, 2933, 2874, 2823, 1754, 1685, 1608, 1545, 1481, 1449 and 1397; δ_H($CDCl_3$) 1.23 [18 H, s, 2 × $(CH_3)_3C$], 2.2–2.5 (2 H, m, 2′-CH_2), 3.07 (2 H, d, *J* 22, CH_2P), 3.42–3.8 (2 H, m, 5′-CH_2), 3.87–4.07 (2 H, m, 4′-H, D_2O exchangeable 3′-OH), 4.27–4.42 (1 H, m, 3′-CH), 5.52–5.87 (4 H, m, 2 × OCH_2O), 6.02–6.15 (1 H, m, 1′-CH), 7.31 (1 H, t, *J* 6, D_2O exchangeable 5′-NH), 7.86 (1 H, s, 6-H) and 9.67 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 38.7; H, 5.1; N, 5.9. $C_{23}H_{35}IN_3O_{12}P \cdot 0.5H_2O$ requires C, 38.8; H, 5.05; N, 5.9%).

5-Iodo-5′-phosphonoacetamido-2′,5′-dideoxyuridine **2**.—*Method A*. A solution of compound **14** (100 mg, 0.14 mmol) in 5% methanolic hydrogen chloride solution (7 cm^3) and water (3 cm^3) was stirred at room temperature for 48 h. The solvent was evaporated under reduced pressure and the residue was purified by chromatography on reverse phase C_{18} silica gel eluting with water to give the *title compound* **2** as a white solid (37 mg, 55%).

Method B.—A solution of compound **14** (150 mg, 0.21 mmol) in methanol (1 cm^3) and hydrochloric acid (5 mol dm^{-3}; 15 cm^3) was stirred at 45 °C for 7 h. The pH of the solution was adjusted to pH 2 by addition of sodium hydroxide solution (1 mol dm^{-3}) and the solvent was evaporated under reduced pressure. The residue was chromatographed on reverse phase C_{18} silica gel eluting with water to give the *title compound* **2** as a white solid (70 mg, 70%), m.p. 168–170 °C decomp.; ν_{max}(KBr)/cm^{-1} 3454, 3303, 3208, 3058, 2932, 2813, 1714, 1669, 1657, 1606, 1563, 1450 and 1405; δ_H[$(CD_3)_2SO$] 1.92–2.37 (2 H, m, 2′-CH_2), 2.25–4.5 (>3 H, br s, D_2O exchangeable OH, H_2O), 2.62 (2 H, d, *J* 22, CH_2P), 3.17–3.5 (2 H, m, 5′-CH_2), 3.65–3.85 (1 H, m, 4′-CH), 4.07–4.25 (1 H, m, 3′-CH), 5.95–6.15 (1 H, m, 1′-CH), 7.8–8.1 (2 H, m, 6-H, D_2O exchangeable 5′-NH) and 11.7 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 27.6; H, 3.3; N, 8.5. $C_{11}H_{15}IN_3O_8P$ requires C, 27.8; H, 3.2; N, 8.8%).

5′-tert-Butyldiphenylsilyl-5-iodo-2′-deoxyuridine **15**.—A solution of 5-iodo-2′-deoxyuridine (5 g, 14.12 mmol) and imidazole (2.12 g, 31.1 mmol) in anhydrous DMF (30 cm^3) was treated with *tert*-butylchlorodiphenylsilane (4.04 cm^3, 15.5 mmol). The mixture was stirred at room temperature for 3 h, and the solvent was evaporated under reduced pressure. The residue was dissolved in chloroform (100 cm^3), extracted with saturated aqueous sodium chloride solution (50 cm^3), dried, and the organic phase was evaporated under reduced pressure. The residue was chromatographed on silica gel eluting with ethyl acetate–hexane (2:1) to give the *title compound* **15** as a white solid (5.24 g, 63%), m.p. 184–186 °C; ν_{max}(KBr)/cm^{-1} 3432, 3069, 2956, 2929, 2856, 1699, 1608, 1477 and 1427; δ_H[$(CD_3)_2SO$] 1.02 [9 H, s, $(CH_3)_3C$], 2.15–2.19 (2 H, m, 2′-CH_2), 3.65–3.95 (3 H, m, 5′-CH_2, 3′-CH), 4.2–4.3 (1 H, m, 4′-CH), 5.3 (1 H, d, D_2O exchangeable 3′-OH), 6.10 (1 H, m, 1′-CH), 7.35–7.7 (10 H, m, 2 × C_6H_5), 7.98 (1 H, s, 6-H) and 11.7 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 50.6; H, 4.75; N, 4.9. $C_{25}H_{29}IN_2O_5Si$ requires C, 50.7; H, 4.9; N, 4.75%).

3′-Benzoyl-5′-tert-butyldiphenylsilyl-5-iodo-2′-deoxyuridine **16**.—A solution of compound **15** (1 g, 1.69 mmol), benzoic anhydride (0.42 g, 1.86 mmol) and 4-*N*,*N*-dimethylaminopyridine (20 mg) in anhydrous pyridine (10 cm^3) was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (50 cm^3) and washed with hydrochloric acid (2 mol dm^{-3}; 2 × 40 cm^3), followed by saturated aqueous sodium hydrogen carbonate solution (2 × 30 cm^3), and saturated aqueous sodium chloride solution (30 cm^3). The organic phase was dried and evaporated under reduced pressure, and the residue, after pre-adsorption onto silica gel, was purified by chromatography

on silica gel eluting with ethyl acetate–hexane (1:3) to give the *title compound* **16** as a white solid (0.94 g, 80%), m.p. 205–208 °C; ν_{max}(KBr)/cm^{-1} 3425, 3186, 3069, 2954, 2929, 2856, 1720, 1695, 1670, 1608, 1450 and 1427; δ_H[$(CD_3)_2SO$] 1.02 [9 H, s, $(CH_3)_3C$], 2.42–2.62 (2 H, m, 2′-CH_2), 3.85–4.02 (2 H, m, 5′-CH_2), 4.25 (1 H, m, 4′-CH), 5.52 (1 H, m, 3′-CH), 6.21 (1 H, m, 1′-CH), 7.3–8.05 (15 H, m, 3 × C_6H_5), 8.09 (1 H, s, 6-H) and 11.79 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 55.0; H, 4.6; N, 4.1. $C_{32}H_{33}IN_2O_6Si$ requires C, 55.2; H, 4.7; N, 4.0%).

3′-Benzoyl-5-iodo-2′-deoxyuridine **17**.—A solution of compound **16** (0.5 g, 0.72 mmol) in THF (5 cm^3) was treated with 5% methanolic hydrogen chloride solution (5 cm^3) and the mixture was stirred at room temperature for 3 h. Additional 5% methanolic hydrogen chloride solution (5 cm^3) was added and, after stirring at room temperature for a further 1 h, the solvent was evaporated under reduced pressure. The residue, after pre-adsorption onto silica gel, was purified by chromatography on silica gel eluting with ethyl acetate–hexane (1:1) to give the *title compound* **17** as a white solid (0.305 g, 92%), m.p. 183–185 °C; ν_{max}(KBr)/cm^{-1} 3434, 3222, 3045, 2926, 2803, 1717, 1685, 1605, 1451 and 1397; δ_H[$(CD_3)_2SO$] 2.32–2.62 (2 H, m, 2′-CH_2), 3.57–3.87 (2 H, m, 5′-CH_2), 4.1–4.3 (1 H, m, 4′-CH), 5.35 (1 H, t, *J* 5, D_2O exchangeable 5′-OH), 5.4–5.6 (1 H, m, 3′-CH), 6.25 (1 H, m, 1′-CH), 7.35–8.15 (5 H, m, C_6H_5), 8.43 (1 H, s, 6-H) and 11.72 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 41.8; H, 3.0; N, 6.0. $C_{16}H_{15}IN_2O_6$ requires C, 41.95; H, 3.3; N, 6.1%).

3′-Benzoyl-5-iodo-5′-sulfamoyl-2′-deoxyuridine **18**.—A solution of compound **17** (1 g, 2.18 mmol) in anhydrous THF (50 cm^3) at 0 °C under nitrogen was treated with a 60% suspension of sodium hydride in oil (262 mg, 7.1 mmol). After stirring at 0 °C for 15 min, the mixture was treated dropwise with a solution of sulfamoyl chloride (580 mg, 4.36 mmol) in anhydrous THF (10 cm^3). The mixture was stirred at 0 °C for 2 h and at room temperature for 24 h. After cooling to 0 °C, the mixture was treated with ethanol (5 cm^3) and the solvent evaporated under reduced pressure. The residue, after pre-adsorption onto silica gel, was purified by chromatography on silica gel eluting with chloroform–methanol (97.5:2.5) to give the *title compound* **18** as a white solid (0.65 g, 56%), m.p. 187 °C decomp.; ν_{max}(KBr)/cm^{-1} 3426, 3232, 3074, 1726, 1679, 1616 and 1450; δ_H[$(CD_3)_2SO$] 2.25–2.75 (2 H, m, 2′-CH_2), 4.25–4.5 (3 H, m, 5′-CH_2, 4′-CH), 5.35–5.55 (1 H, m, 3′-CH), 6.15–6.35 (1 H, m, 1′-CH), 7.42–8.25 (8 H, m, C_6H_5, 6-H, D_2O exchangeable NH_2) and 11.75 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 35.5; H, 3.0; N, 7.7. $C_{16}H_{16}IN_3O_8S$ requires C, 35.8; H, 3.0; N, 7.8%).

5′-Iodo-5′-sulfamoyl-2′-deoxyuridine **19**.—A solution of compound **18** (100 mg, 0.186 mmol) in anhydrous THF (5 cm^3) was treated with a solution of sodium methoxide in methanol (0.5 mol dm^{-3}; 0.74 cm^3, 0.372 mmol). The mixture was stirred at room temperature for 12 h, then neutralised by addition of Amberlite IR 120H ion exchange resin. After filtration, the solvent was evaporated under reduced pressure and the residue was washed with ethyl acetate (3 × 5 cm^3). The resulting solid was filtered, to give the *title compound* **19** as a white solid (48 mg, 60%), m.p. 182–185 °C; ν_{max}(KBr)/cm^{-1} 3444, 3412, 1721, 1635, 1603 and 1456; δ_H[$(CD_3)_2SO$] 2.0–2.32 (2 H, m, 2′-CH_2), 3.87–4.02 (1 H, m, 4′-CH), 4.05–4.3 (3 H, m, 3′-CH, 5′-CH_2), 5.5 (1 H, d, *J* 4, D_2O exchangeable 3′-OH), 6.09–6.14 (1 H, m, 1′-CH), 7.57 (2 H, s, D_2O exchangeable NH_2), 8.01 (1 H, s, 6-H) and 11.65 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 25.4; H, 2.8; N, 9.5. $C_9H_{12}IN_3O_7S$ requires C, 25.0; H, 2.8; N, 9.7%).

3′-Benzoyl-5′-(N-diethoxyphosphoryl)sulfamoyl-5-iodo-2′-deoxyuridine **20**.—A 60% dispersion of sodium hydride in oil (101 mg, 2.5 mmol), was washed with anhydrous hexane under nitrogen and suspended in anhydrous THF (10 cm^3) at 0 °C. The mixture was treated with a solution of compound **18** (450 mg, 0.84 mmol) in anhydrous THF (5 cm^3) and stirred at 0 °C for 15 min. The mixture was then treated with diethyl chlorophosphate (0.193 cm^3, 1.33 mmol) and stirred at 0 °C for 1 h, followed by 48 h at room temperature. After cooling to 0 °C, the mixture was treated with ethanol (5 cm^3) and the solvent was evaporated under reduced pressure. The residue, after pre-adsorption onto silica gel, was purified by chromatography on silica gel eluting with chloroform–methanol (97.5:2.5) of increasing polarity to chloroform–methanol (9:1), to give the *title compound* **20** as a white solid (286 mg, 51%), m.p. 174–176 °C; ν_{max}(KBr)/cm^{-1} 3500, 3080, 2980, 1720, 1620, 1450 and 1390; δ_H[$(CD_3)_2SO$] 1.1–1.22 (6 H, t, *J* 8, 2 × CH_3), 2.25–2.75 (2 H, m, 2′-CH_2), 3.75–4.0 (4 H, m, 2 × CH_2O), 4.05–4.25 (2 H, m, 5′-CH_2), 4.3–4.5 (1 H, m, 4′-CH), 5.45–5.62 (1 H, m, 3′-CH), 6.15–6.3 (1 H, m, 1′-CH), 7.42–8.1 (5 H, m, C_6H_5), 8.22 (1 H, s, 6-H) and 11.74 (1 H, D_2O exchangeable 3-NH) (Found: C, 34.8; H, 3.5; N, 6.0. $C_{20}H_{25}IN_3O_{11}PS·0.67H_2O$ requires C, 35.1; H, 3.8; N, 6.1%).

5′-(N-Diethoxyphosphoryl)sulfamoyl-5-iodo-2′-deoxyuridine **21**. — A solution of compound **19** (200 mg, 0.297 mmol) in THF (10 cm^3) was treated with sodium methoxide in methanol solution (0.5 mol dm^{-3}; 1.19 cm^3, 0.594 mmol) and the mixture was stirred at room temperature for 2 h. The mixture was neutralised by addition of Amberlite IR 120H ion exchange resin, filtered and the solvent was evaporated under reduced pressure. The residue, after pre-adsorption onto silica gel, was purified by chromatography on silica gel eluting with chloroform–methanol (95:5) of increasing polarity to chloroform–methanol (9:1), to give the *title compound* **21** as a white solid (80 mg, 47%), m.p. 169–172 °C; ν_{max}(KBr)/cm^{-1} 3450, 3090, 2980, 1700, 1605 and 1450; δ_H[$(CD_3)_2SO$] 1.1–1.22 (6 H, t, *J* 8, 2 × CH_3), 2.0–2.3 (2 H, m, 2′-CH), 3.75–4.0 (5 H, m, 2 × CH_2, 4′-CH), 4.0–4.1 (2 H, m, 5′-CH_2), 4.25 (1 H, m, 3′-CH), 5.5 (1 H, m, D_2O exchangeable 3′-OH), 6.0–6.2 (1 H, m, 1′-CH), 8.05 (1 H, s, 6-H) and 11.7 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 26.7; H, 3.65; N, 6.8. $C_{13}H_{21}IN_3O_{10}PS·H_2O$ requires C, 26.6; H, 3.9; N, 7.1%).

3′-Benzoyl-5-iodo-5′-0-sulfamoylcarbamoyl-2′-deoxyuridine **22**.—A solution of compound **17** (1 g, 2.18 mmol) in anhydrous acetonitrile (70 cm^3) at −20 °C under nitrogen was treated with chlorosulfonylisocyanate (0.19 cm^3, 2.18 mmol) and the mixture was stirred at −20 °C for 2 h. The mixture was then treated dropwise at −20 °C with a saturated solution of ammonia in acetonitrile until the solution had reached pH 11. The mixture was warmed to room temperature and stirred for 2 h. The solvent was evaporated under reduced pressure and the residue, after pre-adsorption onto silica gel, was purified by chromatography on silica gel eluting with chloroform–methanol (9:1) to give the *title compound* **22** as a white solid (0.96 g, 76%), m.p. 165–167 °C; ν_{max}(KBr)/cm^{-1} 3429, 3247, 3063, 1718, 1667, 1611 and 1452; δ_H[$(CD_3)_2SO$] 2.3–2.8 (2 H, m, 2′-CH_2), 4.1–4.5 (3 H, m, 4′-CH, 5′-CH_2), 5.35–5.55 (1 H, m, 3′-CH), 5.5–7.0 (3 H, br, s, 3 × D_2O exchangeable NH), 6.12–6.3 (1 H, m, 1′-CH), 7.45–8.1 (5 H, m, C_6H_5), 8.15 (1 H, s, 6-H) and 11.7 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 34.6; H, 2.8; N, 9.7. $C_{17}H_{17}IN_4O_9S·0.5\ H_2O$ requires C, 34.65; H, 2.9; N, 9.5%).

5-Iodo-5′-O-sulfamoylcarbamoyl-2′-deoxyuridine **4**.—A solution of compound **22** (300 mg, 0.517 mmol) in methanol (15 cm^3) was treated with sodium methoxide in methanol (0.5 mol dm^{-3}; 2.2 cm^3, 1.03 mmol) and the mixture was stirred at room temperature for 5 h. The mixture was neutralised by addition of Amberlite IR120H ion exchange resin, filtered, and the solvent was evaporated under reduced pressure. The residue was

washed with boiling diethyl ether (4 × 50 cm^3) and crystallised from methanol to give the *title compound* **4** as a white solid (130 mg, 53%), m.p. 176 °C decomp.; ν_{max}(KBr)/cm^{-1} 3421, 3359, 3270, 3085, 2940, 2896, 1745, 1722, 1664, 1611, 1486 and 1456; δ_H[$(CD_3)_2SO$] 1.95–2.45 (2 H, m, 2′-CH_2), 3.9–4.05 (1 H, m, 4′-CH), 4.07–4.35 (3 H, m, 5′-CH_2, 3′-CH), 5.27–5.47 (1 H, d, *J* 4, D_2O exchangeable 3′-OH), 6.02–6.22 (1 H, m, 1′-CH), 7.41 (2 H, s, D_2O exchangeable NH_2), 11.40 (1 H, s, D_2O exchangeable, NH), 8.0 (1 H, s, 6-H) and 11.28 (1 H, s, D_2O exchangeable 3-NH) (Found: C, 25.1; H, 2.5; N, 11.4. $C_{10}H_{13}IN_4O_8S$·0.25 H_2O requires C, 25.0; H, 2.8; N, 11.65%).

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