Synthesis of Uridine Derivatives Containing Strategically Placed Radical Traps as Potential Inhibitors of Ribonucleotide Reductase

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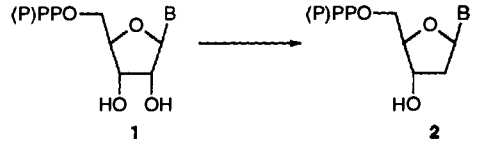
A series of uridine derivatives have been prepared with a view to inhibiting the enzyme ribonucleotide reductase by trapping the radical responsible for initiating the reduction. These have an oxime ether on the *beta* face at C-3 or C-2 of the ribose moiety.

Deoxyribonucleic acid (DNA) synthesis depends on a supply of deoxyribonucleotides. In contrast to ribonucleotides, these are found at low levels in animal cells and so the enzymic reduction of ribonucleotides **1** to deoxyribonucleotides **2** (Scheme 1) is



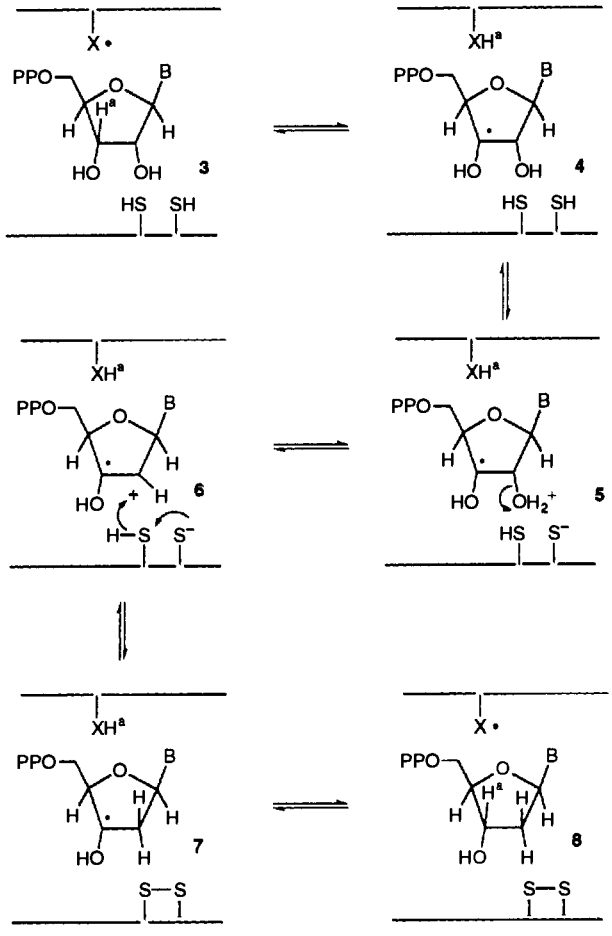
Scheme 1

thought to be a rate-controlling step in the biosynthesis of DNA. The enzymes effecting this reduction, ribonucleotide reductases, are therefore targets in the design of antitumour agents and of antiviral agents.[1]

There are two major classes of ribonucleotide reductases, the coenzyme B_{12}-requiring enzymes, such as that from *Lactobacillus leichmanii*, which reduce nucleoside triphosphates to deoxynucleoside triphosphates; and the iron/tyrosyl radical-requiring enzymes such as those of *Escherichia coli*, mammals, yeast and herpes simplex virus. These reduce nucleoside diphosphates to deoxynucleoside diphosphates. The fact that the *E. coli* enzyme serves as a prototype for mammalian and virally induced enzymes has made it the most studied of all of the ribonucleotide reductases. It is composed of two subunits B_1, (172 kDa) and B_2 (87 kDa), and the active site is at the interface of these subunits. The substrate binds at the larger subunit, B_1, and the cofactor resides in the B_2 subunit. The latter has a binuclear iron centre and a tyrosyl radical.

Studies with [3′-^{3}H]- and [3′-^{2}H]-uridine 5′-diphosphates[2,3] suggested that the *E. coli* enzyme reduction proceeded by radical abstraction of hydrogen from C-3′ in the starting material **3** and return of this same hydrogen to C-3′ to yield the product **8**. The mechanism shown in Scheme 2 was proposed to account for these and other facts. Here a radical in subunit B_2 abstracts the hydrogen, H^a, at C-3′ of the substrate **3** bound to subunit B_1. The resultant radical **4**, on protonation to give cation **5**, encourages dehydration by stabilisation of the radical cation **6**. This is then reduced, as shown, to yield the radical **7** which regains the hydrogen H^a to regenerate the radical centre in the B_2 subunit. The disulfide formed by the reduction is regenerated by a thioredoxin/thioredoxin reductase/NADPH system.

The importance of ribonucleotide reductase in DNA synthesis has led to intensive studies on the inhibition of this enzyme. Based on the mechanism outlined in Scheme 2, we reasoned that a suitably placed radical trap might result in covalent binding with the radical initiator and, since this must interact with H^a at the *beta* face of the ribose moiety, synthesis of a substrate analogue with a radical trap at C-3′ was indicated. Further, since work on 2′-chloro-2′-deoxynucleotides[4] indicated that the 3′-hydrogen abstracted by the enzyme from this substrate analogue was returned to the *beta* face of C-2′, the radical was evidently close to C-3′ and C-2′ at the active site. We therefore resolved to prepare substrate analogues with radical traps at C-2′ as well as C-3′, both on the *beta* face of the sugar moiety or in the plane of the sugar ring.



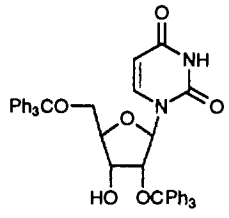
Scheme 2

Corey and others have used oxime ethers[5,6] and alkenes[7,8] in intramolecular free-radical-additions and so we resolved to prepare uridine derivatives with an oxime ether or unsaturated ester or nitrile in the plane of the ring or on the *beta* face at C-3′ or C-2′. These would then be phosphorylated by cellular kinases and tested as inhibitors of the enzyme.

A useful starting point for the synthesis of such compounds would be a protected nucleoside 3′- or 2′-ketone. Since Cook and Moffatt[9] had already prepared the dirityluridine 3′- and 2′-ketones **11** and **12** this seemed a good starting point. We

therefore treated uridine with triphenylmethyl chloride and pyridine using their method[9] and 2',5'-di-*O*-trityluridine **9** was crystallised from the mixture. Further quantities were obtained by chromatography, bringing the total yield to 39%. 3',5'-Di-*O*-trityluridine **10** was also obtained, in 18% yield, from the column.

The protected alcohols were separately oxidised to give the ketones **11** and **12** by the method of Cook and Moffatt[9] but we eventually found it more effective to prepare these by oxidation of the alcohols **9** and **10** using chromium trioxide/pyridine and acetic anhydride.



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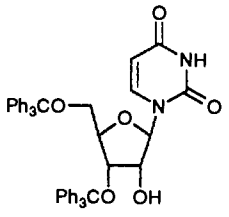

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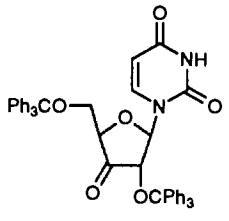

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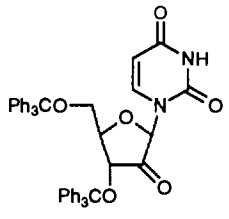

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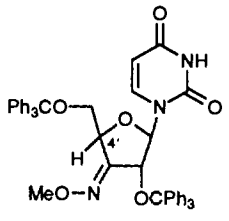

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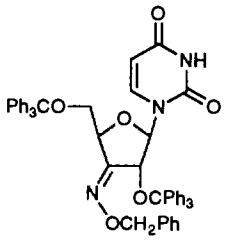

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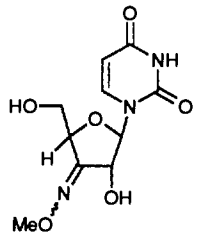

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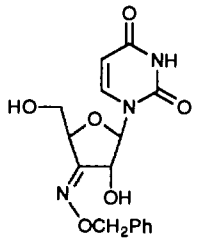

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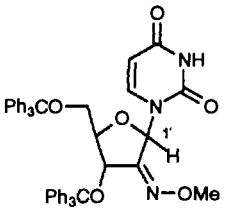
Our first targets were oxime ethers in the plane of the ring. The *O*-methyloxime ether **13** was first prepared from the ketone **11** by heating it with *O*-methylhydroxylamine hydrochloride in pyridine. Only one geometrical isomer of the oxime ether was obtained and irradiation of the three-proton singlet at δ 3.93, due to the OMe protons, caused a nuclear Overhauser enhancement (NOE) of 1% in the broad, one-proton multiplet at δ 4.94. This was unambiguously assigned as 4'-H since, when it was irradiated, the ABX system at δ 3.73 and 3.0 due to 5'-H collapsed to a simple AB system with geminal coupling of 10.1 Hz. Thus the oxime ether was assigned the *E*-configuration shown in structure **13**. When the benzyloxime ether **14** was prepared from the ketone **11** using *O*-benzylhydroxylamine hydrochloride and sodium acetate in refluxing ethanol, there was again only one geometrical isomer formed. Assignment of stereochemistry could again be made from NOE experiments since irradiation of the PhCH_2O signal at δ 5.08 resulted in a 5.3% enhancement of *Ph*CH_2O signal at δ 7.38 and a 0.3% enhancement in a six-proton *ortho*-coupled doublet at δ 7.55 due to *ortho*-protons of one of the trityl groups. Since irradiation of the one-proton doublet at δ 6.10, assigned to 1'-H, resulted in a 0.6% enhancement of the signal at δ 7.55, the latter resonance was assigned to the *ortho*-protons of the 2'-*O*-trityl group. Thus the NOE evidence suggested that the *Z*-oxime ether **14** had been formed.

NOE evidence therefore suggested that the *O*-methyloxime ether exists as the *E*-isomer whilst the *O*-benzyloxime ether exists as the *Z*-isomer. This may be due to the operation of steric effects in the former case and an attractive charge-transfer interaction in the second. When the *O*-methyloxime ether **13** was deprotected by being heated to reflux in aq. acetic acid, the product **15** was found to be a mixture of geometrical isomers whereas deprotection of the benzyloxime ether **14** gave a single isomer tentatively assigned as the *E*-isomer which would be stabilised by hydrogen bonding to the 2'-OH group.

The corresponding 2'-oxime ethers **18** and **19** were prepared from the ketone **12** in similar fashion to the 3'-oxime ethers. Reaction with *O*-methylhydroxylamine hydrochloride and sodium acetate in refluxing ethanol gave a 3:2 ratio of the *Z*- and *E*-isomers **17a** and **17b** respectively, the geometry of the isomers being assigned on the basis of NOE experiments. Irradiation of the OMe signal at δ 3.70 of the major isomer caused a 3% enhancement of the 1'-H signal at δ 6.85 whereas irradiation of the OMe signal of the minor isomer resulted in a small enhancement of the signal assigned to 3'-H. Deprotonation using HCl–CH_2Cl_2 gave the unprotected oxime ether **18** with the altered ratio of geometrical isomers of 4:1. Because of the likelihood of stabilisation of the *E*-isomer **18** by hydrogen bonding to the 3'-hydroxy group, the major isomer was tentatively assigned this configuration. When we attempted to prepare the benzyloxime ether of the ketone **12**, deprotection occurred under the reaction conditions and a single isomer was obtained which was again tentatively assigned the *E*-configuration **19**.

Since acetonitrile was known[10] to trap radicals, we have built this moiety into substrate analogues for ribonucleotide reductase. Thus, reaction of the ketones **11** and **12** with the ylide prepared from diethyl cyanomethylphosphonate and lithium hexamethyldisilazide (LiHMDS) gave the nitriles **20** (R = Ph_3C) and **21** (R = Ph_3C) respectively as single geometrical isomers. The nitrile **20** (R = Ph_3C) was shown to be the *E*-isomer since irradiation of the olefinic proton at δ 4.30 gave an NOE to the multiplet at δ 7.48 assigned to the *ortho* protons of the 2'-*O*-trityl group, an NOE being observed between these and 1'-H signal at δ 6.4 and 2'-H at δ 5.28. The nitrile **21** (R = Ph_3C) was assigned as the *Z*-isomer since irradiation of the olefinic triplet at δ 4.52 showed enhancement of the proton 3'-H at δ 4.98 whose assignment had been confirmed by irradiation of 4'-H at δ 4.33 which decoupled both 3'-H and also the ABX system due to 5'-H at δ 3.25 and 3.05. Deprotection with HCl–CH_2Cl_2 gave the required nitrile **21** (R = H).

The known radical-trapping ability of unsaturated esters[5] made the ester **22** (R = H) an attractive target and so the ketone **12** was treated with the stabilised ylide ethoxycarbonylmethyl(triphenyl)phosphorane to yield ester **22** (R = Ph_3C) as a single isomer. Irradiation of the olefinic triplet signal at δ 5.60 gave a 4% enhancement to the proton 3'-H signal at δ 4.88 and a 3% enhancement to the *ortho*-protons signal of the C-3' *O*-trityl group at δ 7.34. The assignment of 3'-H was confirmed by irradiation of 4'-H signal at δ 4.35, which caused the ABX system at δ 2.90 and 3.13 for the two C-5' protons to become a simple AB system and the 3'-H signal to lose a 5.9 Hz coupling.



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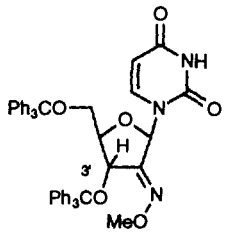

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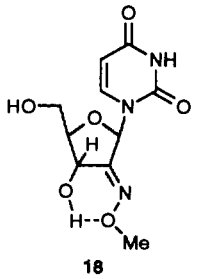

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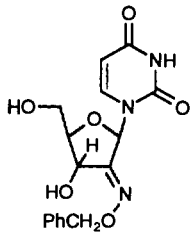

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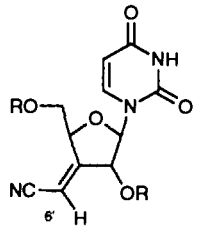

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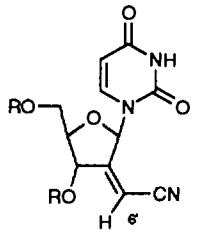

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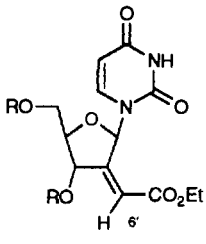

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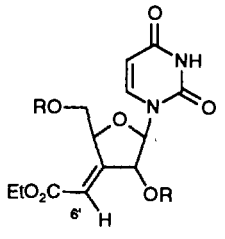


23

Deprotection was again effected using $HCl–CH_2Cl_2$ to yield the target compound **22** (R = H).

The equivalent ester at C-3′ was prepared from the ketone **11** by Wittig reaction with ethoxycarbonylmethyl(triphenyl)-phosphorane to give the protected compound **23** (R = Ph_3C) in 93% yield. This was a single geometric isomer, and irradiation of the olefinic hydrogen signal at δ 5.15 caused the six-proton *ortho* aromatic signal at δ 7.48 to be enhanced. Since irradiation of the doublet of triplets at δ 5.30 (shown to be due to 2′-H by decoupling on irradiation of the doublet due to 1′-H at δ 6.35) also caused this aromatic resonance to be enhanced, it was assigned as the signal due to the *ortho* protons of the 2′-*O*-trityl group and the compound was therefore the *E*-isomer **23** (R = Ph_3C). When the protected compound was left at room temperature with 1% anhydrous trifluoroacetic acid (TFA) in dichloromethane then the monotrityl compound **24** was obtained in 55% yield together with the completely deprotected product **23** (R = H) in 17% yield.

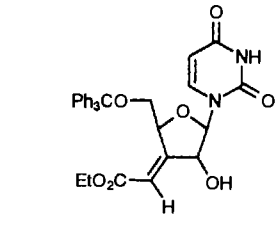
Having prepared a series of compounds structurally similar to dephosphorylated substrates for ribonucleotide reductase but with a radical trap in the plane of the ribose ring, we now proceeded to investigate the preparation of compounds with a trap on the *beta* face of this ring. Having prepared the ester **23** (R = Ph_3C), we argued that reduction or oxidation of the double bond from the less hindered *alpha* face might yield a useful starting point for compounds with a two-carbon chain on the *beta* face. After much unsuccessful work, we found that reduction of the ester **23** (R = Ph_3C) with $LiAlH_4$ gave the alcohol **25** in excellent yield. After failing to achieve oxidation of the double bond by Sharpless methodology, we treated the allylic alcohol with an excess of *m*-chloroperbenzoic acid to yield the epoxide **26** as a single diastereoisomer in 70% yield. On the assumption that the oxidant would attack from the less hindered *alpha* face of the olefin, structure **26** was assigned to the epoxide and this was confirmed by ring opening of the epoxide to the diol **27** in good yield using $LiBH_4$. Here irradiation of the multiplet at δ 1.43 for 6′-H_2 not only caused enhancement of the δ 3.43 proton signal 7′-H_2, but also gave enhancement to the proton 2′-H signal at δ 4.73.

Oxidation of the diol **27** under Pfitzner–Moffatt conditions using the water-soluble carbodiimide 3-[3-(dimethylamino)-propyl]-1-ethylcarbodiimide, and reaction of the intermediate aldehyde *in situ* with *O*-methylhydroxylamine gave a good yield of the oxime ether **28** (R = Ph_3C) as a mixture of geometrical isomers in the ratio 6:4. It was not possible to assign geometry to these experimentally but on the assumption[11] that in aldoximes the formyl proton *anti* to the OR moiety always resonates 0.25–1 ppm downfield from that *syn* to the OR moiety, we have assigned *E*-geometry to the major isomer. Deprotection of the oxime ether **28** (R = Ph_3C) gave the target compound **28** (R = H) as a mixture of geometric isomers.

We now wished to prepare substrate analogues with one carbon on the *beta* face of the ribose moiety and were able to effect methylenation of the ketone **11** by using the ylide methylenetriphenylphosphorane. The product **29** had the expected analytical and spectroscopic properties and the olefinic protons 6′-H^A and 6′-H^B could be assigned since the former showed NOE to 2′-H signal and the latter showed NOE to 4′-H signal, on irradiation. The 2′-methylene analogue **30** could be prepared from the ketone **12** in similar fashion. Attempts to functionalise compounds **29** and **30** by hydroboration, osmylation, *etc.*, were inconclusive and so we prepared the bis-*O*-(*tert*-butyldimethylsilyl)-protected compound **32** *via* the ketone **31** by the method of Samano and Robins.[12] This product was converted into the epoxide **33** by using 2 mol equiv. of *m*-chloroperbenzoic acid. The product was a single diastereoisomer and the expected (3′*R*) configuration was confirmed by irradiation of the 6′-H^B doublet at δ 3.00 which caused NOE not only of the doublet at δ 2.82 due to 6′-H^A but also of the doublet due to 5′-H^A at δ 3.60. The protons 5′-H_2 had been assigned by decoupling experiments. The epimeric epoxide **34** was prepared from the ketone **31** by using Corey's modified Wittig reaction in the expectation that attack of the dimethylsulfoxonium methylide would be from the less hindered *alpha* face of the ketone. The product was different from compound **33** and irradiation of the oxirane proton, 6′-H^B at δ 2.76, caused a substantial NOE to the 4′-H signal at δ 4.13.

A variety of attempts were made to convert the epoxide **33** into compounds from which the target oxime ether **35** might be accessed but without success. We were, however, able to effect ring opening of the epoxide by using lithium acetylide–ethylenediamine complex. The reaction was accompanied by monodeprotection so that the product was the acetylene **36**. A variety of attempts to deprotect this fully were unsuccessful.

The synthetic compounds **15**, **16**, **18**, **19**, **21** (R = H), **22** (R = H), **23** (R = H) and **28** (R = H) have been tested by Glaxo Ltd with ribonucleotide reductase, herpes simplex virus I and cytomegalovirus but showed no activity.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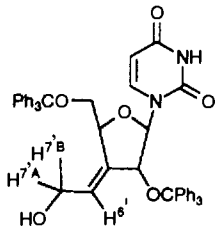
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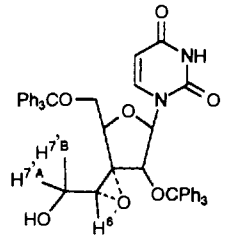
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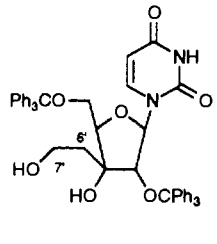
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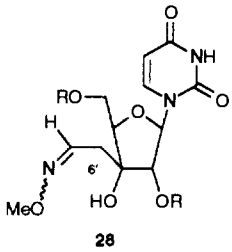
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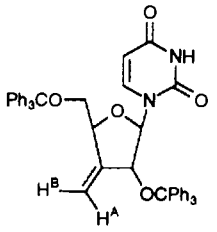
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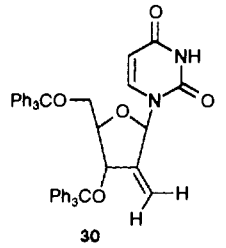
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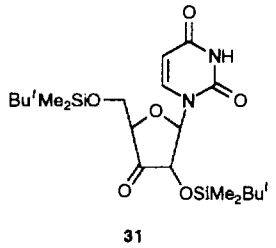
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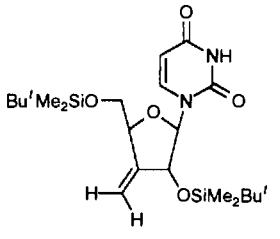
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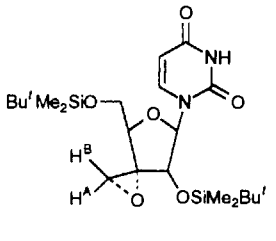
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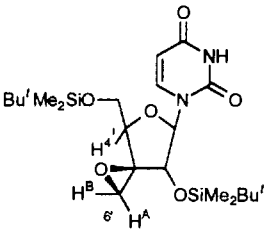
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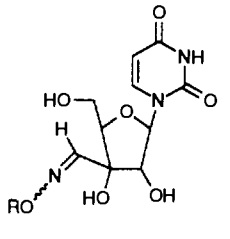
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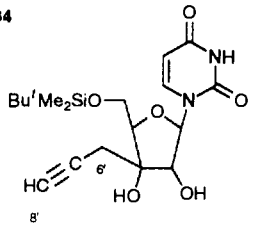
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Experimental

Mps were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer PE241 polarimeter using 1 dm path-length micro cell, and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded on a Perkin-Elmer 1720 Fourier transform instrument. ^{1}H NMR spectra were recorded on Bruker WM360 (360 MHz) or Bruker AMX500 (500 MHz) Fourier transform instruments with $SiMe_4$ as reference. Assignments were confirmed by extensive decoupling experiments. *J* Values are given in Hz. ^{13}C NMR spectra were recorded on a Bruker AMX500 Fourier transform instrument (125.76 MHz) with DEPT experiments as an aid to assigning the ^{13}C resonances, the residual solvent peak being used as reference. Mass spectra were recorded on Kratos MS80 and MS25 instruments by Mr. A. Greenway at Sussex University or on an AutospecQ instrument *via* Dr. R. Storer and Mr. R. Conroy at Glaxo Group Research Ltd. Accurate mass measurements were obtained, using a VG-ZAB-E instrument, by Dr. J. A. Ballantine at SERC Mass Spectrometry Service Centre, Swansea. Microanalyses were either performed by Miss M. Patel at Sussex University or *via* Dr. R. Storer and Mr. R. Conroy at Glaxo Group Research Ltd. TLC was carried out on Merck Kieselgel 60 F254 precoated silica plates of thickness 0.2 mm (ART 5554 and ART 5714). Column chromatography was performed using Merck Kieselgel 60 (230–400 mesh, ART 9385).

3'-Deoxy'-3'-oxo-2',5'-di-O-trityluridine **11**.—Acetic anhydride (236.7 mm^3, 2.45 mmol) and pyridine (388 mm^3, 4.8 mmol) were added to a precooled solution of chromium trioxide (244 mg, 2.5 mmol) in anhydrous dichloromethane (16 cm^3) at 0 °C. The solution was stirred at room temperature for 15 min and a homogeneous black solution was formed. 2',5'-Di-*O*-trityluridine **9** (600 mg, 0.82 mmol), dissolved in dichloromethane (2 cm^3), was added and the solution was stirred for 1 h at room temperature. The black solution was poured into ice-cold ethyl acetate (100 cm^3) and filtered through Celite. The solvent was removed under reduced pressure from the combined organic phases to give a brown gum, which was chromatographed on silica gel, the major component eluting with 10% ethyl acetate in dichloromethane. This was compound **11** as a solid (541 mg, 91%), mp 144–146 °C, with a ^{1}H NMR spectrum identical with that of an authentic sample prepared by the method of Cook and Moffatt.[9]

2'-Deoxy-2'-oxo-3',5'-di-O-trityluridine **12**.—Acetic anhydride (157.8 mm^3, 1.63 mmol) and pyridine (259 mm^3, 3.2 mmol) were added to a precooled solution of chromium trioxide (162.7 mg, 1.6 mmol) in anhydrous dichloromethane (11 cm^3) at 0 °C. The solution was stirred at room temperature for 15 min and a homogeneous black solution was formed. 3',5'-Di-*O*-trityluridine (400 mg, 0.55 mmol), dissolved in dichloromethane (1 cm^3), was added to the above solution, which was stirred for 1 h at room temperature. The black solution was poured into ice-cold ethyl acetate (60 cm^3) and filtered through Celite. The solvent was removed from the combined organic phases under reduced pressure to give a brown gum, which was flash chromatographed on silica gel, the major component eluting with 10% ethyl acetate in dichloromethane to afford compound **12** as a solid (363 mg, 91%), mp 130–137 °C, with an ^{1}H NMR spectrum consistent with the data reported by Cook and Moffatt[9] for compound **12**.

(E)-3'-Deoxy-3'-methoxyimino-2',5'-di-O-trityluridine **13**.—3'-Deoxy-3'-oxo-2',5'-di-*O*-trityluridine **11** (720 mg, 0.99 mmol) and *O*-methylhydroxylamine hydrochloride (400 mg, 4.8 mmol) were dissolved in pyridine (11 cm^3) and the solution was heated to 60 °C for 3.5 h while being stirred. The resultant red viscous

solution was cooled to room temperature and the solvent was removed under reduced pressure to give a dark brown oil. The crude product was dissolved in chloroform (25 cm^3) and the solution was washed successively with dil. aq. hydrochloric acid (2 × 10 cm^3; 0.28 mol dm^{-3}) and saturated brine (10 cm^3) and dried (Na_2SO_4). Filtration and removal of the solvent under reduced pressure afforded a pale yellow foam. The crude product was crystallised from chloroform–ethanol as a *microcrystalline compound* (284 mg, 38%), mp 98–102 °C; $[\alpha]_D^{26}$ +32.4 (*c* 0.5, $CHCl_3$) (Found: C, 76.0; H, 5.8; N, 5.3. $C_{48}H_{41}N_3O_6$ requires C, 76.3; H, 5.4; N, 5.6%); *m/z* (+ve FAB, thioglycerol) 756 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3390 (NH), 1721 and 1698 (C=O); δ_H(360 MHz; C^2HCl_3) 9.19 (1 H, br, exchangeable in ^2H_2O, NH), 7.64 (6 H, m, *J* 8.2, ArH), 7.56 (1 H, d, $J_{6,5}$ 8.3, uracil 6-H), 7.1–7.4 (24 H, ArH), 6.28 (1 H, d, $J_{1',2'}$ 6.8, 1'-H), 5.31 (1 H, dd, $J_{2',1'}$ 6.8, $J_{2',4'}$ 1.3, 2'-H), 5.0 (1 H, d, $J_{5,6}$ 8.3, uracil 5-H), 4.94 (1 H, br, 4'-H), 3.93 (3 H, s, OMe), 3.73 (1 H, dd, $J_{5'A,5'B}$ 10.1, $J_{5'B,4'}$ 2.1, 5'-H^B) and 3.00 (1 H, dd, $J_{5'B,5'A}$ 10.1, $J_{5'A,4'}$ 2.1, 5'-H^A); δ_C (125.76 MHz; C^2HCl_3) 162.5 (C-4CO, uracil), 157.5 (C=N, oxime), 150 (C-2 CO, uracil), 143.8 and 143.0 (*ipso* ArC), 140.1 (C-6), 129.0–127.0 (ArC), 105.0 (C-5), 89.0 and 88.0 (Ph_3C), 87.0 (C-1'), 75.5 and 75.0 (C-2' and -4'), 63.3 (C-5') and 62.5 (C=NO*Me*).

(Z)-3'-*Benzyloxyimino*-3'-*deoxy*-2',5'-*di*-O-*trityluridine* **14**.—*O*-Benzylhydroxylamine hydrochloride (440 mg, 2.76 mmol) was dissolved in ethanol (15 cm^3) and the pH of the solution was adjusted to 5 with sodium acetate (115 mg, 1.39 mmol) using a pH meter. 3'-Deoxy-3'-oxo-2',5'-di-*O*-trityluridine **11** (500 mg, 0.69 mmol) was added and the mixture was heated to reflux for 2 h. A precipitate formed during heating. The solution was cooled and the precipitate was filtered off, dissolved in dichloromethane (25 cm^3) and the solution was washed with water (2 × 10 cm^3) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a semicrystalline solid. Crystallisation from chloroform–ethanol afforded *compound* **14** as microcrystals (515 mg, 90%), mp 97–99 °C; $[\alpha]_D^{28}$ +20.4 (*c* 0.5, $CHCl_3$) (Found: C, 78.0; H, 5.6; N, 4.8. $C_{54}H_{45}N_3O_6$ requires C, 78.0; H, 5.4; N, 5.05%); *m/z* (+FAB, thioglycerol) 832 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3327 (NH) and 1627 (uracil); δ_H(500 MHz; C^2HCl_3) 8.51 (1 H, br d, $J_{NH,5}$ 2.0, exchangeable in ^2H_2O, NH), 7.55 (6 H, m, J_{ortho} 8.2, ArH), 7.38 (5 H, m, ArH), 7.28 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 7.1–7.3 (24 H, overlapping multiplets, ArH), 6.10 (1 H, d, $J_{1',2'}$ 6.7, 1'-H), 5.25 (1 H, dd, $J_{2',1'}$ 6.7, $J_{2',4'}$ 1.5, 2'-H), 5.08 (2 H, s, OCH_2Ph), 4.92 (1 H, br m, 4'-H), 4.90 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.0, uracil 5-H), 3.70 (1 H, dd, $J_{5'A,5'B}$ 10.1, $J_{5'B,4'}$ 1.5, 5'-H^B) and 3.02 (1 H, dd, $J_{5'B,5'A}$ 10.1, $J_{5'A,4'}$ 2.4, 5'-H_A); δ_C(125.76 MHz; C^2HCl_3) 162.7 (C-4CO, uracil), 157.0 (C=N, oxime), 150.0 (C-2CO, uracil), 143.8 and 143.0 (*ipso* ArC), 140.1 (C-6), 137.5 (*ipso* ArC), 128.0–130 (ArC), 102.0 (C-5), 88.9 and 87.4 (Ph_3C), 86.0 (C-1'), 75.8 and 74.6 (C-2' and -4') and 63.0 (C-5').

(E/Z)-3'-*Deoxy*-3'-(*methoxyimino*)*uridine* **15**.—(*E*)-3'-Deoxy-3'-*O*-methoxyimino-2',5'-di-*O*-trityluridine **13** (200 mg, 0.26 mmol) was suspended in 89% aq. acetic acid (20 cm^3) and the suspension was heated to ~ 100 °C using a water-bath for 35 min, after which time the suspended material had dissolved. The solution was allowed to cool to room temperature before removal of the solvent under reduced pressure to furnish a dark brown gum. The crude product was applied to a short column and subjected to flash chromatography on silica gel (12.2 g) with gradient elution starting with ethyl acetate. The triphenylmethanol by-product was eluted with ethyl acetate and the major product (E/Z)-3'-(*methoxyimino*)*uridine* **15** was eluted with 2.5% methanol–ethyl acetate to afford a buff-coloured solid which could not be recrystallised (28 mg, 40%) mp 76–81 °C; $[\alpha]_D^{27}$ +19.4 (*c* 0.8, MeOH); *m/z* (C.I.) 272.0883 ($C_{10}H_{13}N_3O_6$ + H requires *m/z* 272.0885); ν_{max}(film)/cm^{-1} 3385 (NH, OH) and 1687 (C=O); δ_H(500 MHz; 5% $C^2H_3O_2{}^2H$ in C^2HCl_3; *Z*:*E* ratio 4:1) (*Z*-isomer) 7.63 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 5.71 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 5.69 (1 H, d, $J_{1',2'}$ 7.2, 1'-H), 4.86 (1 H, br m, 4'-H), 4.80 (1 H, dd, $J_{2',1'}$ 7.2, $J_{2',4'}$ 1.5, 2'-H), 3.98 (1 H, dd, $J_{5'A,5'B}$ 12.1, $J_{5'B,4'}$ 1.8, 5'-H^B), 3.87 (3 H, s, OMe) and 3.74 (1 H, dd, $J_{5'B,5'A}$ 12.1, $J_{5'A,4'}$ 2.1, 5'-H^A); δ_H(*E*-isomer), 7.5 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 5.79 (1 H, d, $J_{1',2'}$ 4.8, 1'-H), 5.71 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 4.98 (1 H, dd, $J_{2',1'}$ 4.8, $J_{2',4'}$ 1.4, 2'-H), 4.69 (1 H, br q, $J_{4',5'A}$ 3.5, $J_{4',5'B}$ 4.7, 4'-H), 3.87 (4 H, 5'-H^B and OMe) and 3.78 (1 H, dd, $J_{5'A,5'B}$ 12.1, $J_{5'A,4'}$ 3.4, 5'-H^A).

(E)-3'-*Benzyloxyimino*-3'-*deoxyuridine* **16**.—A solution of (*Z*)-3'-benzyloxyimino-3'-deoxy-2',5'-di-*O*-trityluridine **14** (197 mg, 0.23 mmol) in anhydrous dichloromethane (8 cm^3) was cooled to 0 °C. A solution of hydrogen chloride in diethyl ether (0.8 mol dm^{-3}; 1.7 cm^3, 1.36 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. The precipitate was washed several times with diethyl ether (6 × 5 cm^3) and collected by centrifugation before being dried *in vacuo* in a desiccator over potassium hydroxide. The semi-crystalline solid obtained could not be crystallised (45.5 mg, 57%), mp 80–82 °C; $[\alpha]_D^{22}$ +94.0 (*c*. 0.25, MeOH) (Found: C, 55.2; H, 5.1; N, 10.4. $C_{16}H_{17}N_3O_6$ requires C, 55.2; H, 5.2; N, 12.1%); *m/z* (CI) 348.1196 ($C_{16}H_{17}N_3O_6$ + H requires *m/z*, 348.1195); ν_{max}(film)/cm^{-1} 3373 (NH/OH) and 1689 (C=O); δ_H[500 MHz; $(C^2H_3)_2SO$] 11.44 (1 H, br s, exchangeable in ^2H_2O, NH), 7.90 (1 H, d, $J_{5,6}$ 8.1, uracil 6-H), 7.38 (5 H, m, ArH), 6.16 (1 H, d, $J_{2'\text{-}OH,2'}$ 6.4, exchangeable in ^2H_2O, 2'-OH), 5.84 (1 H, d, $J_{1',2'}$ 7.8 1'-H), 5.76 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 5.26 (1 H, t, $J_{5'\text{-}OH,5'A}$ 5.2, $J_{5'\text{-}OH,5B}$ 5.3, exchangeable in ^2H_2O, 5'-OH), 5.14 (2 H, s, OCH_2Ph), 4.88 (1 H, br 4'-H), 4.80 (1 H, br dd, $J_{2',1'}$ 7.8, $J_{2',2'\text{-}OH}$ 6.4, dd in ^2H_2O, 2'-H), 3.84 (1 H, br m, ABX in ^2H_2O, J_{AB} 12, J_{BX}2, 5'-H^B) and 3.66 (1 H, br m, ABX in ^2H_2O, J_{AB} 12, J_{AX} 2, 5'-HA).

(E/Z)-2'-*Deoxy*-2'-*methoxyimino*-3',5'-*di*-O-*trityluridine* **17**.—*O*-Methylhydroxylamine hydrochloride (92 mg, 1.1 mmol) and sodium acetate (46 mg, 0.56 mmol) were dissolved in ethanol (5 cm^3). 2'-Deoxy-2'-oxo-3',5'-di-*O*-trityluridine **12** (200 mg, 0.28 mmol) was added and the mixture was heated to reflux for 2.5 h. After cooling to room temperature the reaction mixture was neutralised dropwise with 1 mol dm^{-3} aq. sodium hydrogen carbonate using a pH meter. The solvent was removed under reduced pressure, the residue was dissolved in dichloromethane (25 cm^3) and the solution was washed successively with water (1 × 10 cm^3) and saturated brine (1 × 10 cm^3) and dried (Na_2SO_4). The solvent was removed under reduced pressure to furnish a foam (99%), which was purified by flash column chromatography on silica gel with 5% ethyl acetate in dichloromethane as eluent. The major product was obtained as a foam in 70% yield. Crystallisation with dichloromethane–hexane was attempted and gave precipitation of an *amorphous solid*, mp 85–97 °C; $[\alpha]_D^{28}$ +62.0 (*c* 0.5, $CHCl_3$ (Found: C, 76.35; H, 5.8; N, 5.5. $C_{48}H_{41}N_3O_6$ requires C, 76.3; H, 5.4; N, 5.6%); *m/z* (+ve FAB; nitrobenzyl alcohol) 756 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 1741 (C=O); δ_H(500 MHz; C^2HCl_3; *Z*:*E* ratio 3:2) (*Z*-isomer) 9.33 (1 H, br, exchangeable in ^2H_2O, NH), 7.61 (1 H, d, $J_{6,5}$ 8.2, uracil 6-H), 7.52 (6 H, m, *J* 8.2, ArH), 7.15–7.3 (24 H, ArH), 6.85 (1 H, s, 1'-H), 5.00 (1 H, br, 3'-H), 4.96 (1 H, d, $J_{5,6}$ 8.2, uracil 5-H), 3.94 (1 H, br, 4'-H), 3.70 (3 H, s, OMe), 3.05 (1 H, dd, $J_{5'A,5'B}$ 10.6, $J_{5'B,4'}$ 2.2, 5'-H^B) and 2.96 (1 H, dd, $J_{5'B,5'A}$ 10.6, $J_{5'A,4'}$ 2.2, 5'-H^A); (*E*-isomer) 9.41 (1 H, br, exchangeable in ^2H_2O, NH), 7.69 (1 H, d, $J_{6,5}$ 8.2, uracil 6-H), 7.46 (6 H, m, *J* 8.2, ArH), 7.15–7.3 (24 H, ArH), 7.25 (1 H, s, 1'-H), 5.10 (1 H, s, 3'-H), 5.08 (1 H, d, $J_{5,6}$ 8.2, uracil 5-H), 3.80 (3 H, s, OMe), 3.56 (1 H, br m, 4'-H), 2.96 (1 H,

dd, $J_{5'A,5'B}$ 10.7, $J_{5'B,4'}$ 2.2, 5'-H^B) and 2.45 (1 H, dd, $J_{5'B,5'A}$ 10.7, $J_{5'A,4'}$ 2.2, 5'-H^A); δ_C(125.76 MHz; C^2HCl_3; both isomers) 163.5 (C-4 CO, uracil), 155 and 153.8 (C=N, oxime), 151 and 150 (C-2 CO uracil), 143.5–142.0 (*ipso* ArC and C-6), 129.5–127.0 (ArC), 102.5 and 102.0 (C-5), 89.0, 88.6, 87.3 and 87.0 (Ph_3C), 84.1 and 83.9 (C-1'), 81.6 and 65.5 and 81.0 and 73.0 (C-3' and -4'), 63.8 and 63.5 (C-5') and 63.3 and 62.5 (C=NO*Me*).

(E/Z)-2'-*Deoxy*-2'-(*methoxyimino*) *uridine* **18**.—A solution of 2'-deoxy-2'-methoxyimino-3',5'-di-*O*-trityluridine **17** (300 mg, 0.40 mmol) in anhydrous dichloromethane (12 cm^3) was cooled to 0 °C. A solution of hydrogen chloride in diethyl ether (0.8 mol dm^{-3}; 2.5 cm^3, 2.0 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. The precipitate thus formed was centrifuged and the supernatant liquid was decanted. The precipitate was washed several times with diethyl ether (6 × 8 cm^3) and collected by centrifugation before being dried *in vacuo* over potassium hydroxide. The *amorphous solid* **18** obtained could not be crystallised (67.2 mg, 62%), mp 100–107 °C; $[\alpha]_D^{27}$ − 27.7 (*c* 1.6, MeOH) (Found: C, 42.8; H, 4.8; N, 14.8. $C_{10}H_{13}N_3O_6$•0.5H_2O requires C, 42.9; H, 5.0; N, 15.0%); *m/z* (CI) 272 ([M + H]$^+$); ν_{max}(film)/cm^{-1} 3393 (NH/OH) and 1688 (C=O); δ_H[360 MHz; $(C^2H_3)_2SO$;*E*/*Z* ratio 8:2]. 11.47 and 11.33 (2 × 1 H, 2 × br, exchangeable in ^2H_2O, NH), 7.60 and 7.53 (2 × 1 H, 2 × d, $J_{6,5}$ 7.9, uracil 6-H), 6.49 and 6.28 (2 × 1 H, 2 × s, 1'-H), 5.67 and 5.62 (2 × 1 H, 2 × dd, $J_{5,6}$ 7.9, $J_{5,NH}$ 2.0, uracil 5-H), 4.67 and 4.64 (2 × 1 H, 2 × s, 3'-H), 3.79 and 3.77 (2 × 3 H, 2 × s, OMe) and 3.74–3.45 (2 × 3 H, br m, 4'-H and 5'-H_2).

(*E*)-2'-*Benzyloxyimino*-2'-*deoxyuridine* **19**.—*O*-Benzylhydroxylamine hydrochloride (330 mg, 2.1 mmol) and sodium acetate (87 mg, 1.0 mmol) were dissolved in ethanol (11 cm^3). 2'-Deoxy-2'-oxo-3',5'-di-*O*-trityluridine **12** (378 mg, 0.52 mmol) was added and the solution was heated to reflux for 3 h. After cooling to room temperature the solution was neutralised dropwise with 1 mol dm^{-3} aq. sodium hydrogen carbonate (1.5 cm^3) using a pH meter. The solvent was removed under reduced pressure to give a pale yellow oil (83%). The ^1H NMR spectrum of the crude product in C^2HCl_3 showed resonances that were typical of the triphenylmethyl group at δ 7.0–7.5 with no other product being present. The aqueous washes were extracted with ethyl acetate (5 × 20 cm^3). The organic extracts were dried (Na_2SO_4) and the filtrate was concentrated under reduced pressure to afford *compound* **19** as a microcrystalline solid that could not be recrystallised (72 mg, 40%), mp 28–31 °C; $[\alpha]_D^{25}$ −52.0 (*c* 0.25, MeOH) (Found: C, 53.8; H, 5.1; N, 11.6. $C_{16}H_{18}N_3O_6$-0.5 H_2O requires C, 54.0; H, 5.05; N, 11.8%); *m/z* (+ve FAB) 348 ([M + H]$^+$); ν_{max}(film)/cm^{-1} 3265 (NH, OH) and 1691 (C=O); δ_H[360 MHz; $(C^2H_3)_2SO$] 7.60 (1 H, d, $J_{5,6}$ 8.0, uracil 6-H), 7.38 (5 H, m, ArH), 6.40 (1 H, s, 1'-H), 5.90 (1 H, t, $J_{3'\text{-}OH,3'}$ 6.8, exchangeable in ^2H_2O, 3'-OH), 5.60 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 5.08 (2 H, q, J_{AB} 12.7, OCH_2Ph), 4.88 (1 H, m, 4'-H), 4.80 (1 H, t, $J_{5'\text{-}OH,5'A}$ 5.7, $J_{5'\text{-}OH,5'B}$ 5.9, exchangeable in ^2H_2O, 5'-OH). 4.70 (1 H, br t, $J_{3',3'\text{-}OH}$ 6.4, $J_{3',4'}$ 6.4, 3'-H) and 3.65–3.5 (3 H, br m, 5'-H_2 and 4'-H).

(E)-3'-*Cyanomethylene*-3'-*deoxy*-2',5'-*di*-O-*trityluridine* **20** (R = Ph_3C).—Diethyl cyanomethylphosphonate (48 mm^3, 0.30 mmol) was added to anhydrous 1,2-dimethoxyethane (DME) (300 mm^3) at room temperature. LiHMDS (1.0 mol dm^{-3} solution in THF; 357 mm^3, 0.36 mmol) was added and the mixture was stirred under nitrogen for 1 h at room temperature before being cooled to −10 °C. 3'-Deoxy-3'-oxo-2',5'-di-*O*-trityluridine **11** (200 mg, 0.27 mmol) as a solution in anhydrous DME (1.3 cm^3) was added dropwise to the precooled solution of the phosphonate under septum conditions. The reaction mixture was allowed to warm to room temperature over a period of 45 min and was stirred under nitrogen at room temperature for 4 h. The solution was quenched dropwise with 10% aq. citric acid (1.8 cm^3) and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (20 cm^3), washed with water (2 × 10 cm^3), and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a pale yellow foam, which was heated with activated charcoal in ethyl acetate until the yellow colour had disappeared. Filtration, and removal of the solvent under reduced pressure, afforded a foam (97%) which was pure according to its ^1H NMR spectrum in C^2HCl_3. Crystallisation from ethanol gave *compound* **20** (R = Ph_3C) as needles (172 mg, 84%), mp 198–200 °C; $[\alpha]_D^{26}$ +96.5 (*c* 0.5, $CHCl_3$) (Found: C, 76.7; H, 5.2; N, 5.3. $C_{49}H_{39}N_3O_5$-H_2O requires C, 76.6; H, 5.3; N, 5.5%); *m/z* (+ve FAB; Me_2SO–EtOH–water) 530.9 ([M − CPh_3 + Na]$^+$); ν_{max}(KBr)/cm^{-1} 3205 (NH), 2250 (CN) and 1690 (C=O); δ_H(360 MHz; C^2HCl_3) 8.88 (1 H, br s, exchangeable in ^2H_2O, NH), 7.54 (1 H, d, $J_{6,5}$ 8.1, uracil 5-H), 7.48 (6 H, m, ArH), 7.1–7.4 (24 H, m, ArH), 6.4 (1 H, d, $J_{1',2'}$ 7.3, 1'-H), 5.28 (1 H, dt, $J_{2',1'}$ 7.3, $J_{2',6'}$ 2.4, $J_{2',4'}$ 2.0, 2'-H), 5.02 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 4.79 (1 H, br s, 4'-H), 4.30 (1 H, t, $J_{6',2'} = J_{6',4'}$ = 2.4, 6'-H), 3.51 (1 H, dd, $J_{5'A,5'B}$ 10.9, $J_{5'B,4'}$ 1.8, 5'-H^B) and 3.20 (1 H, dd, $J_{5'B,5'A}$ 11.1, $J_{5'A,4'}$ 2.3, 5'-H^A); δ_C(125.76 MHz; C^2HCl_3), 162.6 (C-4 CO, uracil), 150.6 (C-2 CO, uracil), 142.9 (*ipso* ArC), 142.8 (C-3'), 139.6 (C-6), 129.0–126.0 (ArC), 114.0 (C≡N), 103.1 (C-5), 95.2 (*C*HC≡N), 88.8 and 87.9 (Ph_3CO), 85.6 (C-1'), 78.6 (C-2'), 76.0–78.0 (C-4') and 64.5 (C-5').

(Z)-2'-*Cyanomethylene*-2'-*deoxy*-3',5'-*di*-O-*trityluridine* **21** (R = Ph_3C).—Diethyl cyanomethylphosphonate (72 mm^3, 0.45 mmol) was added to anhydrous DME (450 mm^3), and LiHMDS (1.0 mol dm^{-3} solution in THF; 624 mm^3, 0.62 mmol) was added. The mixture was stirred under nitrogen for 1 h at room temperature before being cooled to −10 °C. A solution of 2'-deoxy-2'-oxo-3',5'-di-*O*-trityluridine **12** (300 mg, 0.41 mmol) in anhydrous DME (2 cm^3) was added dropwise to the precooled solution of the phosphonate under septum conditions. The solution was allowed to warm to room temperature over a period of 45 min and was stirred under nitrogen at room temperature for 4 h. The solution was quenched dropwise with 10% aq. citric acid (2.5 cm^3) and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (25 cm^3), and the solution was washed with water (2 × 10 cm^3) and dried (Na_2SO_4). The organic solvents were removed under reduced pressure to give a pale yellow foam in 97% yield. The crude product was heated with activated charcoal in ethyl acetate until the yellow colour disappeared. Filtration, and removal of the solvent under reduced pressure, afforded a foam in 85.7% yield. This was pure by ^1H NMR spectroscopy in C^2HCl_3. A sample of *title compound* **21** (R = Ph_3C) was crystallised from dichloromethane–hexane as a microcrystalline compound, mp 130–132 °C; $[\alpha]_D^{27}$ +42.2 (*c* 0.5, $CHCl_3$) (Found: C, 77.25; H, 5.15; N, 5.4. $C_{49}H_{39}N_3O_5$•0.5 H_2O requires C, 77.6; H, 5.3; N, 5.5%); *m/z* (+ve FAB, nitrobenzyl alcohol) 750 ([M + H]$^+$); ν_{max}(KBr)/cm^{-1} 3200 (NH), 2223 (CN) and 1698 (C=O); δ_H(500 MHz, C^2HCl_3) 8.24 (1 H, br, exchangeable in ^2H_2O, NH), 7.50 (1 H, d, $J_{6,5}$ 8.2, uracil 6-H), 7.38 (6 H, m, ArH), 7.1–7.3 (24 H, m, ArH), 6.85 (1 H, t, $J_{1',3'}$ 1.5, $J_{1',6'}$ 1.9, 1'-H), 5.21 (1 H, dd, $J_{5,6}$ 8.2, $J_{5,NH}$ 2.0, uracil 5-H), 4.98 (1 H, dt, $J_{3',4'}$ 5.5, $J_{3',6'}$ 1.9, $J_{3',1'}$ 1.3, 3'-H), 4.52 (1 H, t, $J_{6',3'}$ 1.9, $J_{6',1'}$ 1.5, olefinic), 4.33 (1 H, m, $J_{4',5'A}$ 3.5, $J_{4',5B}$ 2, $J_{4',3'}$ 5.5, 4'-H), 3.25 (1 H, dd, $J_{5'A,5'B}$ 10.7, $J_{5'B,4'}$ 2, 5'-H^B) and 3.05 (1 H, dd, $J_{5'B,5'A}$ 10.7, $J_{5'A,4'}$ 3.5, 5'-H^A); δ_C(125.76 MHz; C^2HCl_3) 162.0 (C-4 CO, uracil), 150.0 (C-2 CO uracil), 143.3 and 142.8 (*ipso*, ArC), 141.0 (C-6), 129.0–126.0 (ArC), 113.0 (C≡N), 103.0 (C-5), 97.4 (*C*HC≡N), 89.0 and 87.4 (Ph_3C), 84.6 (C-1'), 83.9 and 74.4 (C-3' and -4') and 63.3 (C-5').

(Z)-2′-*Cyanomethylene*-2′-*deoxyuridine* **21** (R = H).—A solution of 2′-cyanomethylene-2′-deoxy-3′,5′-di-*O*-trityluridine **21** (R = Ph_3C) (154 mg, 0.20 mmol) in anhydrous dichloromethane (6 cm^3) was cooled to 0 °C. A solution of hydrogen chloride in diethyl ether (0.8 mol dm^{-3}; 1.3 cm^3, 1.0 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. The precipitate thus formed was centrifuged and the supernatant liquid was decanted. The precipitate was washed several times with diethyl ether (6 × 4 cm^3) and collected by centrifugation before being dried *in vacuo* over potassium hydroxide. The title compound, an amorphous solid, could not be crystallised (31.6 mg, 60%), mp 92–94 °C; $[\alpha]_D^{27}$ −124.0 (*c* 0.05, MeOH) (Found: C, 48.3; H, 4.3; N, 14.5. $C_{11}H_{11}N_3O_5$·0.5 H_2O requires C, 48.2; H, 4.4; N, 15.3%); *m/z* (+ve CI, NH_3) 266 ($[M + H]^+$); *m/z* (+ve FAB, nitrobenzyl alcohol) 266 ($[M + H]^+$); ν_{max}(film)/cm^{-1} 3366 (OH, NH), 2226 (CN) and 1688 (C=O); δ_H[360 MHz; $(C^2H_3)_2SO$)] 8.00 (1 H, br d, $J_{NH,5}$ 2.0, exchangeable in ^2H_2O, NH), 7.60 (1 H, d, $J_{6,5}$ 8.0, uracil 6-H), 6.51 (1 H, t, $J_{1',3'}$ 2.0, $J_{6',1'}$ 2.5, 1′-H), 5.90 (1 H, t, $J_{6',1'}$ and $J_{6',3'}$ 2.5, olefinic), 5.75 (1 H, dd, $J_{5,6}$ 8.0, $J_{5,NH}$ 2.0, uracil 5-H), 4.67 (1 H, dt, $J_{3',1'}$ 2.0, $J_{3',4'}$ 5.6, $J_{3',6'}$ 2.5, 3′-H), 3.70 (1 H, m, 4′-H), 3.65 (1 H, dd, $J_{5'A,5'B}$ 12.0, $J_{5'B,4'}$ 2.0 5′-H^B) and 3.51 (1 H, dd, $J_{5'B,5'A}$ 12.0, $J_{5'A,4'}$ 3.4, 5′-H^A).

(Z)-2′-*Deoxy*-2′-*ethoxycarbonylmethylene*-3′,5′-*di*-O-*trityluridine* **22** (R = CPh_3).—2′-Deoxy-2′-oxo-3′,5′-di-*O*-trityluridine **12** (100 mg, 0.14 mmol) and ethoxycarbonylmethylene(triphenyl)phosphorane (96 mg, 0.28 mmol) were dissolved in anhydrous tetrahydrofuran (THF) (1.65 cm^3) and the solution was heated to reflux for 5 h while being stirred. The solution was cooled to room temperature and the solvent was removed under reduced pressure to furnish a pale yellow foam (186 mg). The crude product was subjected to flash chromatography on silica gel and the major component was eluted with 10% ethyl acetate in dichloromethane. The eluate was concentrated under reduced pressure to give a foam (84%) which was a pure compound according to its ^1H NMR spectrum run in C^2HCl_3. The foam thus obtained was crystallised from dichloromethane–hexane to furnish the *title compound* as a microcrystalline compound (38 mg, 34%), mp 125–128 °C; $[\alpha]_D^{26}$ −20 (*c* 0.65, $CHCl_3$) (Found: C, 76.8; H, 5.6; N, 3.25. $C_{51}H_{44}N_2O_7$ requires C, 76.9; H, 5.5; N, 3.5%); *m/z* (+ve FAB; 3-nitrobenzyl alcohol) 797 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3353 (NH) and 1697 (C=O); δ_H(500 MHz; C^2HCl_3) 8.48 (1 H, br, exchangeable in ^2H_2O, NH), 7.34 (6 H, m, ArH), 7.2–7.1 (24 H, m, ArH), 7.10 (1 H, d, $J_{6,5}$ 8.0, uracil 6-H), 6.90 (1 H, t, $J_{1',6'}$ 2.0, $J_{1',3'}$ 1.8, 1′-H), 5.60 (1 H, t, $J_{6',1'}$ 2.0, $J_{6',3'}$ 2.1, 6′-H), 5.25 (1 H, dd, $J_{5,6}$ 8.3, $J_{5,NH}$ 2, uracil 5-H), 4.88 (1 H, dt, $J_{3',4'}$ 5.9, $J_{3',6'}$ 2.1, 3′-H), 4.35 (1 H, m, 4′-H), 4.07 (2 H, q, *J* 7.1, OCH_2Me), 3.13 (1 H, dd, $J_{5'A,5'B}$ 10.5, $J_{5'B,4'}$ 2.7, 5′-H^B), 2.90 (1 H, dd, $J_{5'B,5'A}$ 11.0, $J_{5'B,4'}$ 2.5, 5′-H^A) and 1.22 (3 H, t, *J* 7.1, OCH_2Me).

(Z)-2′-*Deoxy*-2′-(*ethoxycarbonylmethylene*)*uridine* **22** (R = H).—A solution of 2′-deoxy-2′-ethoxycarbonylmethylene-3′,5′-di-*O*-trityluridine **22** (R = CPh_3) (160 mg, 0.20 mmol) in anhydrous dichloromethane (6 cm^3) was cooled to 0 °C. A solution of hydrogen chloride in diethyl ether (0.8 mol dm^{-3}; 1.6 cm^3, 1.3 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. The precipitate thus formed was centrifuged and the supernatant liquid was decanted. The precipitate was then washed several times with diethyl ether (6 × 4 cm^3) and collected by centrifugation before being dried *in vacuo* over potassium hydroxide. The amorphous solid thus obtained could not be crystallised (40.5 mg, 64%), mp 80–83 °C; $[\alpha]_D^{29}$ −100.8 (*c* 1.1, MeOH); *m/z* (CI) 313.1036 ($C_{13}H_{16}N_2O_7$ + H requires *m/z*, 313.1035); ν_{max}(film)/cm^{-1} 3250 (OH, NH), 1723 and 1699 (C=O); δ_H[360 MHz; $(C^2H_3)_2SO$] 11.3 (1 H, s, NH), 7.50 (1 H, d, $J_{6,5}$ 8.0, uracil 6-H), 6.60 (1 H, t, $J_{1',6'}$ = $J_{1',3'}$ = 2.0, 1′-H), 6.01 (1 H, t, $J_{6',1'}$ 2.0, $J_{6',3'}$ 2.1, 6′-H), 5.55 (1 H, dd, $J_{5,6}$ 8.3, uracil 5-H), 4.90 (1 H, dt, $J_{3',1'}$ 2.0, $J_{3',4'}$ 6.2, $J_{3',6}$ 2.1, 3′-H), 4.70 (1 H, m, 4′-H), 4.07 (2 H, q, *J* 7.1, OCH_2Me), 3.70 (1 H, dd, $J_{5'A,5'B}$ 10.2, $J_{5'B,4'}$ 4.6, 5′-H^B), 3.50 (1 H, dd, $J_{5'B,5'A}$ 10.2, $J_{5'A,4'}$ 4.6, 5′-H^A) and 1.12 (3 H, t *J* 7.1, OCH_2Me).

(E)-3′-*Deoxy*-3′-*ethoxycarbonylmethylene*-2′,5′-*di*-O-*trityluridine* **23** (R = Ph_3C).—3′-Deoxy-3′-oxo-2′,5′-di-*O*-trityluridine **11** (600 mg, 0.83 mmol) and ethoxycarbonylmethylene(triphenyl)phosphorane (600 mg, 1.7 mmol) were dissolved in anhydrous THF (15 cm^3) and the solution was heated and heated to reflux for 5 h. The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure to furnish a pale yellow foam (186 mg). The crude product was crystallised from ethanol to furnish a microcrystalline compound (462 mg, 70%). The mother liquors were concentrated under reduced pressure and the residue was subjected to flash chromatography on silica gel with 10% ethyl acetate in dichloromethane to yield further quantities of the *title product* as a solid (151 mg, 23%), which could be crystallised from dichloromethane–ethanol, mp 256–259 °C; $[\alpha]_D^{25}$ +79.2 (*c* 0.5, $CHCl_3$) (Found: C, 76.6; H, 5.5; N, 3.5. $C_{51}H_{44}N_2O_7$ requires C, 76.9; H, 5.5; N, 3.5%); ν_{max}(KBr)/cm^{-1} 3379 (NH), 1712 and 1693 (C=O); δ_H(360 MHz; C^2HCl_3) 8.20 (1 H, br d, $J_{NH,5}$ 2, exchangeable in ^2H_2O, NH), 7.48 (6 H, m, J_{ortho} 8.1, ArH), 7.15–7.28 (25 H, m, ArH + uracil 6-H), 6.35 (1 H, d, $J_{1',2'}$ 7.5, 1′-H), 5.30 (1 H, dt, $J_{2',1'}$ 7.5, $J_{2',4'}$ = $J_{2',6}$ = 2.1, 2′-H), 5.25 (1 H, m, 4′-H), 5.15 (1 H, t, $J_{6',2'}$ 2.0, $J_{6',4'}$ 2.1, olefinic), 5.05 (1 H, dd, $J_{5,NH}$ 2, $J_{5,6}$ 8.1, uracil 5-H), 4.00 (2 H, q, *J* 7.1, OCH_2), 3.60 (1 H, dd, $J_{5'A,5'B}$ 10.1, $J_{5'B,4'}$ 2.0, 5′-H^B), 3.10 (1 H, dd, $J_{5'B,5'A}$, 10.1, $J_{5'A,4'}$ 2.0, 5′-H^A) and 1.15 (3 H, t, *J* 7.1, OCH_2Me).

(E)-3′-*Deoxy*-3′-*ethoxycarbonylmethylene*-5′-O-*trityluridine* **24** *and* (Z)-3′-*Deoxy*-3′-(*ethoxycarbonylmethylene*)*uridine* **23** (R = H).—3′-Deoxy-3′-ethoxycarbonylmethylene-2′,5′-di-*O*-trityluridine **23** (R = Ph_3C) (500 mg; 0.63 mmol) was dissolved in dichloromethane (75 cm^3). Anhydrous TFA (760 mm^3, 9.9 mmol) was added and the solution was stirred at room temperature for 20 min before the addition of 1 mol dm^{-3} aq. sodium hydrogen carbonate (45 cm^3) and vigorous stirring of the heterogeneous solution. The yellow colour disappeared. The organic layer was washed with water (2 × 25 cm^3) and with saturated brine (20 cm^3) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a foam (351 mg, 70%), which was chromatographed on silica gel by gradient elution starting with dichloromethane. The triphenylmethanol by-product was eluted first and the major product was eluted with 100% ethyl acetate to give a solid. Crystallisation from dichloromethane afforded microcrystals of 3′-*deoxy*-3′-[(E)-*ethoxycarbonylmethylene*]-5′-O-*trityluridine* **24** (193 mg, 55%), mp 95–97 °C; $[\alpha]_D^{23}$ +159.7 (*c* 0.35, $CHCl_3$) (Found: C, 69.6; H, 5.9; N, 4.9. $C_{32}H_{30}N_2O_7$ requires C, 69.3; H, 5.4; N, 5.0%); *m/z* (+ve FAB; 3-nitrobenzyl alcohol) 555 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3398 (NH, OH) and 1698 (C=O); δ_H[360 MHz; $(C^2H_3)_2SO$] 10.00 (1 H, br d, $J_{NH,5'}$ 2.0, exchangeable in ^2H_2O, NH), 7.30 (1 H, d, $J_{6',5'}$ 8.1, uracil 6-H), 7.45–7.15 (15 H, m, ArH), 6.38 (1 H, d, $J_{2'\text{-}OH,2'}$ 6.3, exchangeable in ^2H_2O, 2′-OH), 5.95 (1 H, t, $J_{6',2'}$ 2.0, $J_{6',4'}$ 2.4, 6′-H), 5.77 (1 H, d, $J_{1',2'}$ 8.0, 1′-H), 5.46 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2, uracil 5-H), 5.30 (1 H, br m, 4′-H), 4.88 (1 H, br m, 2′-H), 4.05 (2 H, m, *J* 7.1, OCH_2Me), 3.67 (1 H, dd, $J_{5'A,5'B}$ 10.0, $J_{5'B,4'}$ 3.6, 5′-H^B), 3.13 (1 H, dd, $J_{5'B,5'A}$ 10.0, $J_{5'A,4'}$ 1.8, 5′-H^A) and 1.15 (3 H, t, *J* 7.1, OCH_2Me).

The aqueous washes from the reaction mixture work-up were combined and extracted with ethyl acetate (4 × 40 cm^3). The extracts were dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure to furnish (*Z*)-3′-deoxy-

3'-(ethoxycarbonylmethylene)uridine **23** (R = H) (33 mg, 17%) as a solid, mp 85–88 °C; $[\alpha]_D^{23}$ +37.4 (*c* 0.5, MeOH); *m/z* (CI) 313.1036 ($C_{13}H_{16}N_2O_7$ + H requires *m/z*, 313.1035); ν_{max}(KBr)/cm^{-1} 3384 (NH, OH) and 1689 (C=O); δ_H[360 MHz; $(C^2H_3)_2SO$] 10.05 (1 H, br, exchangeable in ^2H_2O, NH), 7.95 (**1** H, d, $J_{6',5'}$ 8.1, uracil 6-H), 6.20 (1 H, d, $J_{1',2'}$ 6.2, 1'-H), 5.85 (1 H, t, $J_{6',2'}$ 2.3, $J_{6',4'}$ 2.0, 6'-H), 5.75 (1 H, d, $J_{2'\text{-OH},2'}$ 8.0, 2'-OH), 5.70 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 5.20 (1 H, t, $J_{5'\text{-OH},5'A}$ 5.3, $J_{5'\text{-OH},5'B}$ 5.3, 5'-OH), 5.15 (1 H, br, 4'-H), 4.63 (1 H, br m, 2'-H), 4.15 (2 H, q, *J* 7.1, OC*H*$_2$Me), 3.83 (1 H, br m, 5'-H^B), 3.68 (1 H, br m, 5'-H^A) and **1**.23 (3 H, t, *J* 7.1, OCH$_2$*Me*).

3'-*Deoxy*-3'-(2-*hydroxyethylidene*)-2',5'-*di*-O-*trityluridine* **25**.—3'-Deoxy-3'-ethoxycarbonylmethylene-2',5'-di-*O*-tritylurid-ine **23**. (R = Ph_3C) (538 mg, 0.68 mmol) was dissolved in anhydrous THF (18 cm^3). Lithium aluminium hydride (81 mg, 2.1 mmol) was added very slowly to this solution at 0 °C in such a way that effervescence of the reaction solution was minimised. The reaction solution was stirred at room temperature for 40 min and was then cooled to 0 °C. Water (81 mm^3), 15% aq. sodium hydroxide (81 mm^3) and water (242 mm^3) were added carefully dropwise in succession. The grey granular solid that formed was filtered off on Celite. The solvent was removed under reduced pressure to furnish a glass in 93% yield. This could be used without further purification in the next step. Crystallisation from ethyl acetate–hexane afforded *compound* **25** as a microcrystalline compound (400 mg, 78%), m.p. 119–121 °C; $[\alpha]_D^{26}$ +34.1 (*c* 0.16, $CHCl_3$) (Found: C, 78.0; H, 5.6; N, 3.7. $C_{49}H_{42}N_2O_6$ requires C, 78.0; H, 5.6; N, 3.7%); *m/z* (+ve FAB; Me_2SO–EtOH–water) 777.8 ([M + Na]$^+$); ν_{max}(KBr)/cm^{-1} 3396 (NH) and 1693 (C=O); δ_H(360 MHz; 5% $C^2H_3O^2H$ in C^2HCl_3) 7.60 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 7.43 (6 H, m, J_{ortho} 8.2, ArH), 7.35–7.15 (24 H, m, ArH), 6.18 (1 H, d, $J_{1',2'}$ 7.1, 1'-H), 5.18 (1 H, br dt, $J_{2',1'}$ 7.1, 2'-H), 5.05 (1 H, m, $J_{6',2'}$ 2.1, $J_{6',4'}$ 1.7, $J_{6',7B}$ 8.7, $J_{6',7A}$ 5.0, 6'-H), 4.95 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 4.73 (1 H, br 4'-H), 3.88 (1 H, dd, $J_{7'B,7'A}$ 14.1, $J_{7'B,6'}$ 8.7, 7'-H^B), 3.75 (1 H, dt, $J_{7'A,7'B}$ 14.1, $J_{7'A,2'}$ 2.3, $J_{7'A,6'}$ 5.0, 7'-H^A), 3.18 (1 H, dd, $J_{5'B,5'A}$ 10.5, $J_{5'B,4'}$ 1.9, 5'-H^B) and 3.01 (1 H, dd, $J_{5'A,5'B}$ 10.5, $J_{5'A,4'}$ 2.2, 5'-H^A).

3',6'-*Anhydro*-3'-(1,2-*dihydroxyethyl*)-2',5'-*di*-O-*trityluridine* **26**.—3'-Deoxy-3'-(2-hydroxyethylidene)-2',5'-di-*O*-tritylurid-ine **25** (1.83 g, 2.42 mmol) was dissolved in dichloromethane (65 cm^3) and *m*-chloroperbenzoic acid (3.019 g, 8.75 mmol; ~ 50% acid tech. grade) was added. The solution was stirred for 48 h at room temperature. The organic solution was washed successively with 10% aq. sodium hydrogen carbonate (4 × 40 cm^3), water (40 cm^3) and saturated brine (40 cm^3). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure at below 35 °C to afford a foam (1.8 g, 97%). Crystallisation from dichloromethane–hexane furnished the title microcrystalline compound (1.3 g, 70%), mp 255–257 °C; $[\alpha]_D^{28}$ +52.9 (*c* 0.75, $CHCl_3$) (Found: C, 75.2; H, 5.7; N, 3.2. $C_{49}H_{42}N_2O_7$ requires C, 76.3; H, 5.45; N, 3.6%); *m/z* (+ve FAB; Me_2SO–EtOH–water) 794.8 ([M + H + Na]$^+$); ν_{max}(KBr)/cm^{-1} 3312 (OH/NH) and 1702 (C=O); δ_H(500 MHz; C^2HCl_3) 8.45 (1 H, br d, $J_{NH,5}$ 2.1, exchangeable in ^2H_2O, NH), 7.45 (1 H, d, $J_{6',5'}$ 8.1, uracil 6-H), 7.4–7.2 (30 H, m, ArH), 6.35 (1 H, d, $J_{1',2'}$ 7.6, 1'-H), 5.10 (1 H, d, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.1, uracil 5-H), 4.9 (1 H, d, $J_{2',1'}$ 7.6, 2'-H), 4.10 (1 H, t, $J_{4',5'B}$ 3.1, $J_{4',5'A}$ 2.3, 4'-H), 3.40 (1 H, br dt, $J_{7'B,7'A}$ 13.0, $J_{7'B,6'}$ 2.2, 7'-H^B), 3.30 (1 H, dd, $J_{5'B,5'A}$ 11.1, $J_{5'B,4'}$ 3.1, 5'-H^B), 3.08 (1 H, dd, $J_{5'A,5'B}$ 11.1, $J_{5'A,4'}$ 2.3, 5'-H^A), 3.00 (1 H, br m, $J_{7'A,7'B}$ 13.0, $J_{7'A,7'\text{-OH}}$ 4.3, 7'-H^B), 1.80 (1 H, t, $J_{6',7'B}$ 3.2, $J_{6',7'A}$ 3.8, 6'-H) and 1.55 (1 H, br t, $J_{7'\text{-OH},7'B}$ 2.3, $J_{7'\text{-OH},7'A}$ 4.3, 7'-OH).

3'-(2-*Hydroxyethyl*)-2',5'-*di*-O-*trityluridine* **27**.—Epoxide **26** (1.67 g, 2.2 mmol) was dissolved in anhydrous THF (98 cm^3) and lithium boranuide (1.38 g, 63 mmol) was added. The reaction was heated to reflux for 6 h, the solution was cooled to 0 °C and excess of lithium boranuide was decomposed by dropwise addition of 10% aq. citric acid (46 cm^3). The pH of the solution was 5–6 using a pH meter. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (100 cm^3). The organic solution was washed with water (50 cm^3) and saturated brine (50 cm^3), and was then dried (Na_2SO_4). The solvent was removed under reduced pressure to yield a foam (1.61 g, 95%). Column chromatography of the crude product on silica gel deactivated with water (30% v/v) and elution with 40% ethyl acetate in dichloromethane afforded a solid (1.2 g, 70%). Crystallisation from ethyl acetate–hexane furnished *compound* **27** as prisms, mp 228–230 °C; $[\alpha]_D^{28}$ +44.0 (*c* 0.5, $CHCl_3$) (Found: C, 74.7; H, 5.7; N, 3.4. $C_{49}H_{44}N_2O_7 \cdot H_2O$ requires C, 74.4; H, 5.7; N, 3.6%); *m/z* (+ve FAB; 3-nitrobenzyl alcohol) 773 ([M + H]$^+$); ν_{max}(KBr)/cm^{-1} 3260 (OH/NH) and 1700 (C=O); δ_H(360 MHz; C^2HCl_3) 8.38 (1 H, br d, $J_{NH,5}$ 2.3, exchangeable with $2H_2O$, NH), 7.48–7.23 (30 H, m, ArH), 7.05 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 5.78 (1 H, d, $J_{1',2'}$ 4.5, 1'-H), 5.28 (1 H, dd, $J_{5,6}$ 8.0, $J_{5,NH}$ 2.3, uracil 5-H), 4.73 (1 H, d, $J_{2',1'}$ 4.6, 2'-H), 4.05 (1 H, q, $J_{4',5'B}$ 5.3, $J_{4',5'A}$ 5.7, 4'-H), 3.43 (2 H, br m, 7'-H$_2$), 3.38 (1 H, dd, $J_{5'B,5'A}$ 10.5, $J_{5'B,4'}$ 5.3, 5'-H^B), 3.35 (1 H, br t, $J_{7'\text{-OH},7'A}$ < 2, exchangeable in ^2H_2O, 7'-OH), 3.23 (1 H, dd, $J_{5'A,5'B}$ 10.2, $J_{5'A,4'}$ 5.7, 5'-H^A) and 1.43 (2 H, br m, 6'-H$_2$).

3'-[2-(*Methoxyimino*)*ethyl*]-2',5'-*di*-O-*trityluridine* **28** (R = Ph_3C).—3'-(2-Hydroxyethyl)-2',5'-di-*O*-trityluridine **27** (300 mg, 0.39 mmol) was dissolved in anhydrous dimethyl sulfoxide (3.95 cm^3). To this solution was added 1-[3-(dimethyl-amino)propyl]-3-ethylcarbodiimide hydrochloride (229 mg, 1.19 mmol) followed by successive addition of pyridine (39.5 mm^3, 0.49 mmol) and TFA (197 mm^3, 0.25 mmol). After the mixture had been stirred for 20 h at room temperature, pyridine (3.95 cm^3) was added followed by *O*-methylhydroxylamine hydrochloride (126 mg, 1.5 mmol). The reaction solution was stirred for a further 20 h at room temperature. After this time dichloromethane (30 cm^3) was added and the solution was washed successively with 10% aq. citric acid (20 cm^3), 1 mol dm^{-3} aq. sodium hydrogen carbonate (20 cm^3) and saturated brine (20 cm^3). The extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a pale yellow oil. The crude product was subjected to flash chromatography on silica gel deactivated with water (30% v/v) and elution with 40% ethyl acetate in dichloromethane. A glass was obtained (274 mg, 88%). Crystallisation from ethyl acetate–dichloromethane afforded the *title microcrystalline compound*, mp 128–132 °C; $[\alpha]_D^{28}$ +44.0 (*c* 0.2, $CHCl_3$) (Found: C, 74.6; H, 6.1; N, 4.9. $C_{50}H_{45}N_3O_7$ requires C, 75.1; H, 5.6; N, 5.2%); *m/z* (+ve FAB; 3-nitrobenzyl alcohol) 800 ([M + H]$^+$); ν_{max}(KBr)/cm^{-1} 3300 (OH) and 1700 (C=O); δ_H(360 MHz; C^2HCl_3; 3:2 ratio *E*:*Z* isomers) (*E*-isomer) 10.65 (1 H, br exch. d, $J_{NH,5}$ 2.1, exchangeable in ^2H_2O, NH), 7.46–7.18 (31 H, m, ArH and 7'-H), 7.05 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 5.93 (1 H, d, $J_{1',2'}$ 4.5, 1'-H), 5.26 (1 H, d, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.1, uracil 5-H), 4.45 (1 H, d, $J_{2',1'}$ 4.5, 2'-H), 4.03 (1 H, t, $J_{4',5'B}$ 5.1, $J_{4',5'A}$ 4.2, 4'-H), 3.61 (3 H, s, OMe), 3.29 (2 H, m, $J_{5'B,5'A}$ 11.2, $J_{5'A,4'}$ 3.6, $J_{5'B,4'}$ 4.0, 5-H$_2$), 3.24 (1 H, exch. s, 3'-OH) and 1.95 (2 H, br m, 6'-H$_2$); (*Z*-isomer) 10.50 (1 H, br d, $J_{NH,5}$ 2.1, exchangeable in ^2H_2O, NH), 7.46–7.18 (30 H, m, ArH), 7.05 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 6.43 (1 H, t, $J_{7',6'B}$ 6.1, $J_{7',6'A}$ 5.4, 7'-H), 6.05 (1 H, d, $J_{1',2'}$ 5.3, 1'-H), 5.18 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 4.28 (1 H, d, $J_{2',1'}$ 5.4, 2'-H), 4.06 (1 H, t, $J_{4',5'B}$ 5.1, $J_{4',5'A}$ 5.4, 4'-H), 3.68 (3 H, s, OMe), 3.25 (1 H, dd, $J_{5'B,5'A}$ 11.0, $J_{5'B,4'}$ 5.2, 5'-H^B), 3.15 (1 H, dd $J_{5'A,5'B}$ 11.0, $J_{5'A,4'}$ 5.1, 5'-H^A), 3.11 (1 H, exch. s, 3'-OH), 1.95 (1 H, dd, $J_{6'B,6'A}$ 15.0, $J_{6'B,7'}$ 6.0, 6'-H^B) and 1.83 (1 H, dd, $J_{6'B,6'A}$ 15.0, $J_{6'A,7'}$ 5.4, 6'-H^A).

3'-[2-(*Methoxyimino)ethyl*]*uridine* **28** (R = H).—3'-[2-(Methoxyimino)ethyl]-2',5'-di-*O*-trityluridine **28** (R = Ph_3C) (200 mg, 0.25 mmol) was dissolved in dichloromethane (8 cm^3). A solution of hydrogen chloride in diethyl ether (0.8 mol dm^{-3}; 1.7 cm^3, 1.36 mmol) was added dropwise and the solution was stirred at 0 °C for 1 h. The precipitate thus formed was centrifuged out and the supernatant liquid was decanted. The precipitate was washed several times with diethyl ether (6 × 5 cm^3) and collected by centrifugation before being dried in a desiccator *in vacuo* over potassium hydroxide. The buff-coloured amorphous solid obtained could not be crystallised (50 mg, 63%), mp 93–95 °C; $[\alpha]_D^{27}$ +13.2 (*c* 0.25, MeOH); *m/z* (+ve FAB; 3-nitrobenzyl alcohol) 316 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3380 (OH/NH) and 1691 (C=O); δ_H[360 MHz; $(C^2H_3)_2SO$; *E*:*Z* ratio 1:1] 9.80 (2 × 1 H, br d, $J_{NH,5}$ 2.1, exchangeable in ^2H_2O, NH), 8.05 (2 × 1 H, 2 × d, $J_{6,5}$ 8.1, uracil 6-H), 7.50 (1 H, t, $J_{7',6'A}$ 6.6, $J_{7',6'B}$ 5.8, 7'-H, *E*-isomer), 7.28 (2 × 1 H, d, $J_{1',2'}$ 7.7, 1'-H), 7.21 (2 × 1 H, d, $J_{2',1'}$ 7.8, 2'-H), 7.0 (1 H, t, $J_{7',6'A} = J_{7',6'B}$ = 4.7, 7'-H, *Z*-isomer), 5.90 (2 × 1 H, q, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.1, uracil 5-H), 5.68 (2 × 1 H, 2 × br m, 4'-H), 3.90 (2 H, dd, $J_{6'A,B}$, 11.5, $J_{6'A,7'}$ 6.0, 6'-H_2, *E*-isomer), 3.84 and 3.72 (6 H, 2 × s, OMe), 3.50 (2 × 2 H, $J_{5'A,B}$ 12, $J_{5'A,4'}$ 2.2, $J_{5'B,4'}$ 2.2, 5'-H_2, both isomers) and 2.63 (2 H, d, *J* 4.7, 6'-H_2, *Z*-isomer).

3'-*Deoxy*-3'-*methylene*-2',5'-*di*-O-*trityluridine* **29**.—Hexamethyldisilazane (121 mm^3, 0.57 mmol) was added to anhydrous THF (3 cm^3) under nitrogen and the solution was cooled to −78 °C before the addition of butyllithium (1.85 mol dm^{-3} solution in hexane; 310 mm^3, 0.57 mmol). The stirred solution was allowed to warm to −50 °C over a period of 30 min. Methyltriphenylphosphonium bromide (186 mg, 0.52 mmol), suspended in anhydrous THF (3 cm^3), was added to the LiHMDS solution at −50 °C under septum conditions. The solution immediately became yellow and the phosphorane solution was allowed to warm to room temperature over a period of 1 h and was stirred at room temperature for a further 30 min. A solution of 3'-deoxy-3'-oxo-2',5'-di-*O*-trityluridine **11** (363 mg, 0.5 mmol) in anhydrous THF (2 cm^3) was cooled to −78 °C and the phosphorane solution was added dropwise by cannular transfer at −78 °C. A precipitate formed immediately concomitant with the disappearance of the yellow colour of the phosphorane. The reaction mixture was allowed to warm to room temperature during 1.5 h. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (10 cm^3) and the solution was washed successively with dil. aq. hydrochloric acid (2 × 5 cm^3; 0.28 mol dm^{-3}), water (2 × 5 cm^3) and saturated brine (5 cm^3) and dried (Na_2SO_4). The solvent was removed under reduced pressure to furnish a pale yellow foam (325 mg, 90%), which was crystallised from ethanol to give *compound* **29** as needles (242 mg, 67%), mp 196–199 °C; $[\alpha]_D^{28}$ +52 (*c* 0.5, $CHCl_3$) (Found: C, 79.2; H, 5.65; N, 3.9. $C_{48}H_{40}N_2O_5$ requires C, 79.55; H, 5.5; N, 3.9%); *m/z* (+ve FAB; EtOH–3-nitrobenzyl alcohol) 725 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3414 (NH) and 1693 (C=O); δ_H(360 MHz; C^2HCl_3) 8.73 (1 H, br d, $J_{NH,5}$ 2.0, exchangeable in ^2H_2O, NH), 7.50 (6 H, m, *J* 8.1, ArH), 7.41 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 7.4–7.2 (24 H, m, ArH), 6.20 (1 H, d, $J_{1',2'}$ 4.9, 1'-H), 5.05 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.0, uracil 5-H), 4.94 (1 H, m, $J_{2',1'}$ 4.9, $J_{2',4'}$ 1.4, $J_{2',6'A} = J_{2',6'B}$ = 1.5, 2'-H), 4.83 (1 H, distorted t, $J_{6'B,6'A}$ 3.7, $J_{6'B,2'} = J_{6'B,4'}$ = 1.5, 6'-H^B), 4.67 (1 H, br m, 4'-H), 4.50 (1 H, distorted t, $J_{6'A,6'B}$ 3.7, $J_{6'A,2'} = J_{6'A,4'}$ = 1.5, 6'-H^A), 3.28 (1 H, dd, $J_{5'A,5'B}$ 10.5, $J_{5'B,4'}$ 2.8, 5'-H^B) and 3.10 (1 H, dd, $J_{5'B,5'A}$ 10.5, $J_{5'A,4'}$ 2.8, 5'-H^A).

2'-*Deoxy*-2'-*methylene*-3',5'-*di*-O-*trityluridine* **30**.—Methyltriphenylphosphonium bromide (393 mg, 1.1 mmol) was suspended in anhydrous diethyl ether (16 cm^3). LiHMDS (1.0 mol dm^{-3} solution in THF; 2.36 cm^3, 2.36 mmol) was added to this suspension and the resultant yellow solution was stirred at room temperature for 2 h before being cooled to −78 °C, and a solution of 2'-deoxy-2'-oxo-3',5'-di-*O*-trityluridine **12** (400 mg, 0.55 mmol) in anhydrous diethyl ether (5 cm^3) was added dropwise at −78 °C under septum conditions. A precipitate formed immediately and the yellow colour of the phosphorane solution diminished. The reaction mixture was allowed to warm to −10 °C over a period of 1.5 h and was kept at −5 to 0 °C for 48 h, After this time the reaction was quenched with saturated aq. ammonium chloride (10 cm^3). The aqueous layer was separated and extracted with diethyl ether (3 × 15 cm^3). The combined ether layers were washed with water (2 × 15 cm^3) and saturated brine and dried (Na_2SO_4). Filtration of the organic solution, followed by removal of the solvent under reduced pressure, gave rise to a pale yellow foam, which was subjected to flash chromatography with silica gel. Elution with 30% ethyl acetate in dichloromethane gave *compound* **30** as an amorphous solid which was analytically pure (362 mg, 91%), mp 192–193 °C; $[\alpha]_D^{26}$ +43 (*c* 0.4, $CHCl_3$) (Found: C, 78.3; H, 5.4; N, 3.7. $C_{48}H_{40}N_2O_5 \cdot 0.5\ H_2O$ requires C, 78.6; H, 5.6; N, 3.8%); *m/z* 725 ($[M + H]^+$); ν_{max}(KBr)/cm^{-1} 3404 (NH) and 1697 (C=O); δ_H(360 MHz, C^2HCl_3) 9.15 (1 H, br d, $J_{NH,5}$ 2.0, exchangeable in ^2H_2O, NH), 7.56 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 7.50 (~6 H, m, ArH), 7.4–7.2 (24 H, m, ArH), 6.85 (1 H, s, 1'-H), 5.05 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.0, uracil 5'-H), 5.00 (1 H, d, $J_{6'B,6'A}$ 1.5, 6'-H^B), 4.65 (1 H, d, $J_{6'A,6'B}$ 1.5, 6'-H^A), 3.80 (1 H, br m, 4'-H), 4.65 (1 H, s, 3'-H), 3.00 (1 H, dd, $J_{5'A,5'B}$ 10.5, $J_{5'B,4'}$ 2.4, 5'-H^B) and 2.65 (1 H, dd, $J_{5'B,5'A}$ 10.5, $J_{5'A,4'}$ 2.9, 5'-H^A); δ_C(125.76 MHz; C^2HCl_3) 162.5 (C-4 CO, uracil), 151.0 (C-2 CO, uracil), 146.0–142.0 (ArC), 142.9 (C-6'), 130.0–127.0 (ArC), 115.3 (C-7'), 102.3 (C-5'), 88.4 and 87.3 (CPh_3), 84.6 (C-1'), 84.0 and 75.1 (C-3' and -4'), 81.9 (C-6) and 63.6 (C-5).

3',6'-*Dehydro*-2',5'-*di*-O-(tert-*butyldimethylsilyl*)-3'-(*hydroxymethyl*)*uridine* **33**.—3'-Deoxy-2',5'-di-O-(*tert*-butyldimethylsilyl)-3-methyleneuridine **32**[12] (330 mg, 0.70 mmol) was dissolved in dichloromethane (1.8 cm^3) and MCPBA (4.86 mg, 1.4 mmol; ~50% acid tech. grade) was added. The mixture was stirred for 48 h at room temperature, dichloromethane (60 cm^3) was added and the organic solution was washed successively with 10% aq. sodium metabisulfite ($Na_2S_2O_5$) (3 × 30 cm^3), 10% aq. sodium hydrogen carbonate (3 × 30 cm^3), water (30 cm^3) and saturated brine (30 cm^3). The organic layer was dried (Na_2SO_4) and the solvent was removed under reduced pressure below 35 °C to afford the *title compound* as a foam (330 mg, 97%); $[\alpha]_D^{27}$ +50.8 (*c* 0.5, $CHCl_3$) (Found: C, 55,0; H, 8.5; N, 5.3. $C_{22}H_{40}N_2O_6Si_2$ requires C, 54.5; H, 8.3; N, 5.8%); *m/z* (CI) 485.2503 ($C_{22}H_{40}N_2O_6Si_2$ + H requires *m/z*, 485.2503); ν_{max} (KBr)/cm^{-1} 3210 (NH) and 1698 (C=O); δ_H(360 MHz; C^2HCl_3) 9.31 (1 H, br d, $J_{NH,5}$ 2.0, exchangeable in ^2H_2O, NH), 7.80 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 6.10 (1 H, d, $J_{1',2'}$ 5.5, 1'-H), 5.73 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.0, uracil 5-H), 4.23 (1 H, d, $J_{2',1'}$ 5.8, 2'-H), 4.13 (1 H, br, 4'-H), 3.95 (1 H, dd, $J_{5'A,5'B}$ 11.7, $J_{5'B,4'}$ 2.1, 5'-H^B), 3.60 (1 H, d, $J_{5'A,5'B}$ 11.7, 5'-H^A), 3.0 (1 H, d, $J_{6'B,6'A}$ 4.5 6'-H^B), 2.82 (1 H, d, $J_{6'B,6'A}$ 4.5, 6'-H^A), 1.1–0.80 (18 H, overlapping, Bu^t) and 0.08–0.02 (12 H, overlapping, MeSi). Peaks corresponding to a minor product were also present.

1-[3',6'-*Anhydro*-2',5'-*di*-O-(tert-*butyldimethylsilyl*)-3'-*hydroxymethyl*-β-D-*xylofuranosyl*]*uracil* **34**.— Trimethylsulfoxonium chloride (93 mg, 0.72 mmol) was suspended in anhydrous THF (4 cm^3). LiHMDS (1 mol dm^{-3} solution in THF; 729 mm^3, 0.729 mmol) was added and the solution was stirred for 1 h at room temperature under nitrogen to allow the chloride to dissolve. 3'-Deoxy-2',5'-di-*O*-(*tert*-butyldimethylsilyl)-3-oxouridine **31**[12] (137 mg, 0.29 mmol) was dissolved in anhydrous THF (4 cm^3) and cooled to −78 °C. The

dimethylsulfoxonium methylide solution was added dropwise to this solution at −78 °C. The mixture was allowed to warm to room temperature over a period of 1.5 h and was then heated at 50 °C for 2 h. After cooling of the red solution to room temperature, saturated aq. ammonium chloride (10 cm^3) was added. The aqueous layer was extracted with dichloromethane (2 × 10 cm^3) and the combined organic extracts were washed with water (3 × 10 cm^3) and saturated brine (5 cm^3) and were then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a dark orange foam, which was chromatographed on silica gel. Elution with 20% ethyl acetate in dichloromethane afforded the title compound as a yellow gum (80 mg, 57%); $[\alpha]_D^{27}$ +30.0 (*c* 0.6, $CHCl_3$); *m/z* 485.2503 ($C_{22}H_{40}N_2O_6Si_2$ + H requires *m/z*, 485.2503); $\nu_{max}(CHCl_3)/cm^{-1}$ 3203 (NH) and 1697 (C=O); δ_H(360 MHz; C^2HCl_3) 8.58 (1 H, br, exchangeable in ^2H_2O, NH), 8.00 (1 H, d, $J_{6,5}$ 8.1, uracil 6-H), 6.13 (1 H, d, $J_{1',2'}$ 6.7, 1'-H), 5.75 (1 H, dd, $J_{5,6}$ 8.1, $J_{5,NH}$ 2.0, uracil 5-H), 4.33 (1 H, d, $J_{2',1'}$ 6.7, 2'-H), 4.13 (1 H, br m, 4'-H), 3.85 (1 H, dd, $J_{5'A,5'B}$ 11.7, $J_{5'B,4'}$ 2.8, 5'-H^B), 3.68 (1 H, dd, $J_{5'B,5'A}$ 11.7, $J_{5'A,4'}$ 1.9, 5'-H^A), 3.15 (1 H, d, $J_{6'A,6'B}$ 5.3, 6'-H^A), 2.76 (1 H, d, $J_{6'B,6'A}$ 5.3, 6'-H^B), 1.1–0.80 (18 H, overlapping Bu^t) and 0.08–0.02 (12 H, overlapping SiMe).

5'-O-(tert-*Butyldimethylsilyl*)-3'-(*prop*-2-*ynyl*)*uridine* **36**.—3',6'-Anhydro-2',5'-di-*O*-(*tert*-butyldimethylsilyl)-3'-(hydroxymethyl)uridine **33** (250 mg, 0.52 mmol) was dissolved in anhydrous THF (10 cm^3). The solution was cooled to 0 °C and lithium acetylide–ethylenediamine complex (709 mg, 7.7 mmol) was added. The mixture was stirred under N_2 for 1 h at 0 °C and for a further 3 h at room temperature. After this time the reaction mixture was cooled to 0 °C and quenched cautiously, dropwise, with 10% aq. citric acid (3.2 cm^3). The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (15 cm^3). The organic solution was washed with water (2 × 10 cm^3) and saturated brine (10 cm^3), and was dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a brown foam, which was applied to a column under flash conditions using silica gel deactivated with water (50% v/v). Elution with 50% ethyl acetate in dichloromethane gave compound **36** as a yellow solid (98 mg, 48%), mp 94–97 °C; $[\alpha]_D^{24}$ +23.4 (*c* 0.175, $CHCl_3$) (Found: C, 53.0; H, 7.3; N, 6.7. $C_{18}H_{28}N_2O_6Si{\cdot}0.5H_2O$ requires C, 53.3; H, 7.2; N, 6.9%); *m/z* (CI; NH_3) 397 ($[M + H]^+$): ν_{max} ($CHCl_3$)/cm^{-1} 3309 (NH), 2180w (C≡C) and 1688 (C=O); δ_H (360 MHz; C^2HCl_3) 7.87 (1 H, d, $J_{6,5}$ 8.1, uridine 6-H), 6.00 (1 H, d, $J_{1',2'}$ 6.7, 1'-H), 5.75 (1 H, d, $J_{5,6}$ 8.1, uracil 5-H), 4.27 (1 H, br m, 4'-H), 4.13 (1 H, d, $J_{2',1'}$ 6.7, 2'-H), 4.03 (1 H, dd, $J_{5'A,5'B}$ 12.0, $J_{5'B,4'}$ < 1.6, 5'-H^B), 3.90 (1 H, dd, $J_{5'B,5'A}$ 12, $J_{5'A,4'}$ 1.6, 5'-H^A), 2.75 (1 H, dd, $J_{6'B,6'A}$ 17, $J_{6'B,8'}$ 2.1, 6'-H^B), 2.63 (1 H, dd, $J_{6'B,6'A}$ 17, $J_{6'A,8'}$ 2.1, 6'-H^A), 2.10 (1 H, t, $J_{8',6'B}$ $J_{8',6'A}$ 2.1, acetylenic H), 1.1–0.80 (9 H, overlapping Bu^t) and 0.08–0.02 (6 H, overlapping SiMe).

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