Synthesis of the Carbocyclic Analogue of the Antiviral Nucleoside (*E*)-5-(2-Bromovinyl)-2′-deoxyuridine

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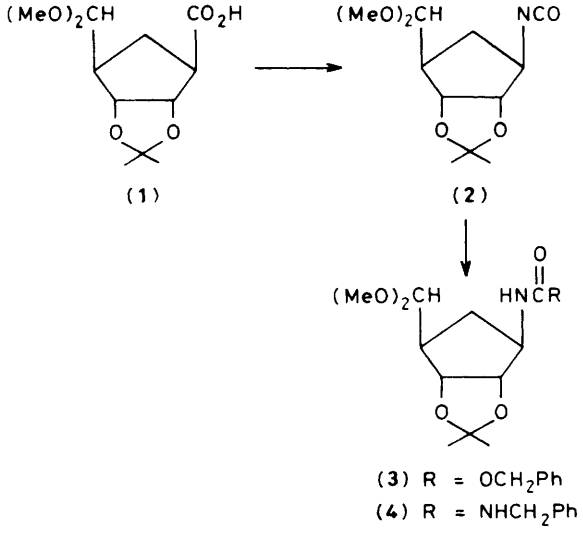
The cyclopentanecarboxylic acid (**1**) was converted *via* the isocyanate (**2**) and the urea (**5**) into carbocyclic uridine (**12**). Similarly, the α- and β-epimers of carbocyclic 2′-deoxyuridine, (**19a**) and (**19b**), were synthesized from the acids (**13**). Compounds (**19b**) and (**19a**) were further modified to afford carbocyclic (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (**25b**) and its α-epimer (**25a**), respectively.

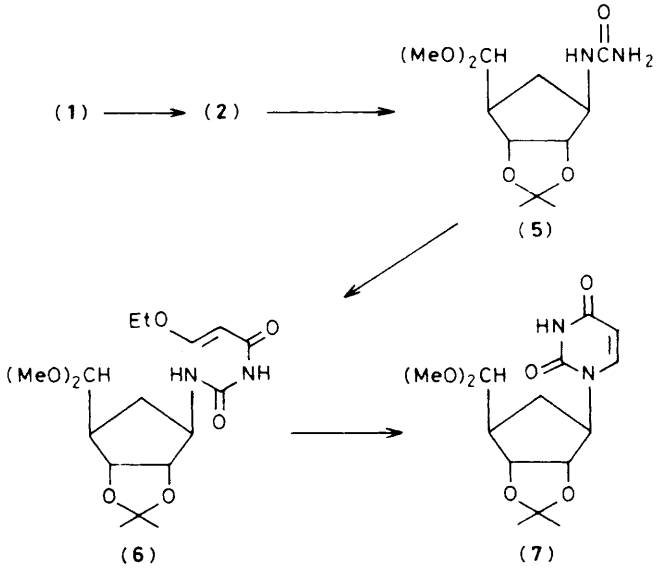
Several 5-substituted -2′-deoxyuridines exhibit good antiherpes activity.[1] Foremost among this class of compound is (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) which possesses potent and selective activity against herpes simplex virus (HSV) type-1.[2] It is of considerable interest to prepare the corresponding carbocyclic analogue of BVDU, a compound which is not subject to *in vivo* deactivation by phosphorolytic cleavage.[3] This paper describes new syntheses of carbocyclic uridine and 2′-deoxyuridine leading to the preparation of carbocyclic BVDU. Recently, Shealy *et al.* have reported that carbocyclic 5-halogeno-2′-deoxyuridines possess good activity *in vitro* against HSV-1 and HSV-2.[4]

The use of the cyclopentanecarboxylic acids (**1**) and (**13**)[5] for the synthesis of carbocyclic *N*-nucleoside analogues required, in each case, conversion of the carboxy group into a suitable nitrogen-containing derivative. The mild conditions for Curtius rearrangement of a carboxy group into an isocyanate with diphenylphosphoryl azide (DPPA)[6] were particularly suitable in not endangering the acetal and isopropylidene protecting groups. Thus, DPPA and triethylamine in boiling benzene converted the acid (**1**) into the isocyanate (**2**) and on subsequent addition of either benzyl alcohol or benzylamine, the carbamate (**3**) or urea (**4**) was obtained, respectively (Scheme 1).

Treatment of the isocyanate (**2**) with ammonia gas gave the crude urea (**5**) which was not isolated, but acylated directly with (*E*)-3-ethoxypropenoyl chloride in pyridine to afford the substituted urea (**6**). Addition of a catalytic amount of



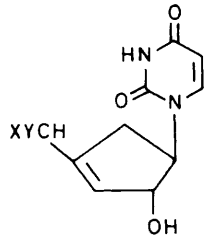
Scheme 1.



Scheme 2.

4-(dimethylamino)pyridine (DMAP) greatly accelerated the acylation stage. Cyclization to the uracil (**7**) was smoothly effected by aqueous ammonia, in 59% overall yield from (**5**) (Scheme 2).

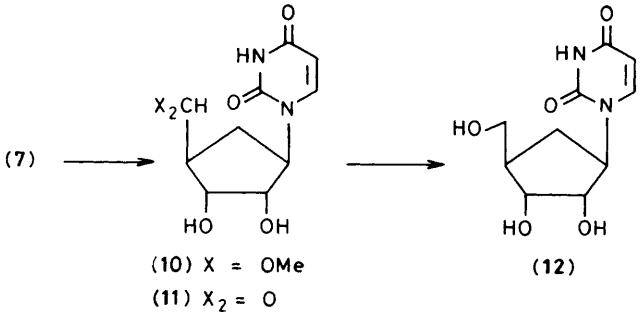
Unfortunately, the deprotection sequence was not as straightforward as with imidazopyridine carbocyclic *C*-nucleosides.[5] Attempted hydrolysis of the acetal function with acidic acetone appeared to cause elimination of the isopropylidene group. In fact, when the uracil (**7**) was heated under reflux in 80% acetic acid, the α,β-unsaturated aldehyde (**8**) was obtained. Reduction of compound (**8**) with sodium borohydride afforded the cyclopentene nucleoside analogue (**9**). This opened a possible



(**8**) XY = O
(**9**) X = OH, Y = H

pathway to carbocyclic 3′-deoxyuridines, but their known lack of biological activity[4] discouraged further development of this route.

Although we were unable to remove the acetal group selectively, this difficulty was overcome by removal of the isopropylidene group with acidic methanol, to give the diol (**10**), and then hydrolysis of the dimethyl acetal with 80% acetic acid at 80 °C for 15 min. Finally, reduction of the aldehyde (**11**) with sodium borohydride gave (±)-carbocyclic uridine (**12**)[7] (Scheme 3).

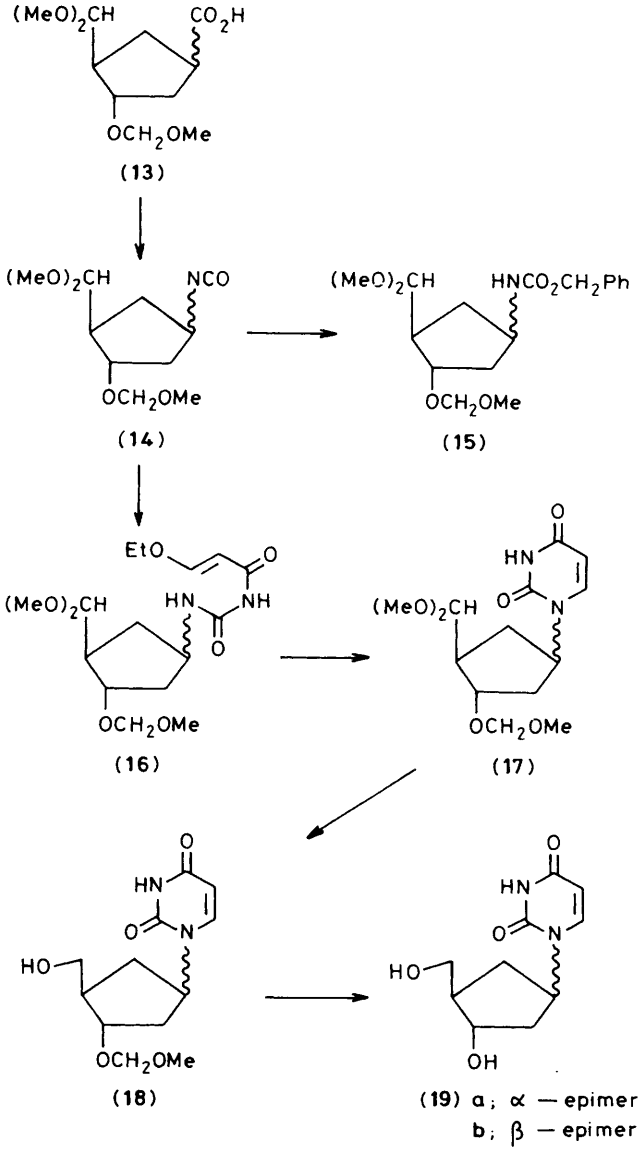


Scheme 3.

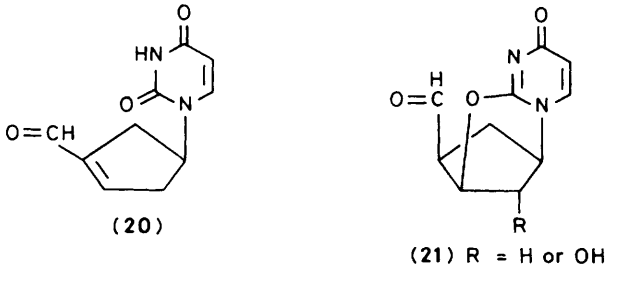
Treatment of the acid (**13**) with DPPA followed by benzyl alcohol afforded the expected carbamate (**15**). The intermediate isocyanate (**14**) was directly converted into the urea (**16**) by reaction first with ammonia gas and then with (*E*)-3-ethoxypropenoyl chloride as described above. Cyclization in aqueous ammonia gave the uracil derivative (**17**). Selective hydrolysis of the acetal function was accomplished with 80% acetic acid at 80 °C for 15 min, and reduction of the resulting aldehyde gave the alcohol (**18**). Subsequent removal of the methoxymethyl protecting group with a catalytic amount of hydrochloric acid in boiling methanol furnished the epimeric (±)-carbocyclic 2′-deoxyuridines (**19a** and **b**) which were separated by short-path column chromatography (Scheme 4). Assignment of the configuration at C-1′ was made by comparison of epimer (**19b**) (n.m.r., u.v., and mass spectra, and m.p.) with carbocyclic 2′-deoxyuridine prepared *via* an alternative route.[7,8]

The elimination reaction of the uracil (**17**) to give the aldehyde (**20**) was effected in boiling aqueous acetic acid, although a much longer reaction time was needed than for the corresponding isopropylidene derivative (**7**). ^{1}H N.m.r. spectra and t.l.c. confirmed that both epimers of compound (**17**) formed the same product (**20**). The fact that this elimination was not observed with the imidazo[1,5-*a*]pyridine carbocyclic *C*-nucleosides suggests involvement of the uracil moiety; although there is no supporting evidence it is possible that a cyclonucleoside intermediate[9] [*e.g.* (**21**)] is implicated.

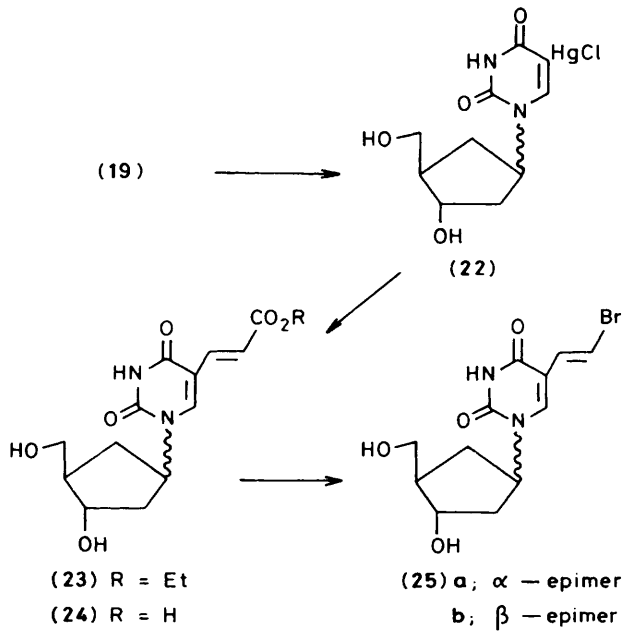
In order to complete the synthesis of carbocyclic BVDU, we followed the route established by Jones *et al.*[10] for the conversion of 2′-deoxyuridine into BVDU. Mercuriation at the 5-position of the uracil ring according to the procedure of Bergstrom and Ruth[11] afforded the chloromercurio intermediates (**22**) in 56% yield. We did not attempt to characterize this compound, but we directly treated it with ethyl acrylate in the presence of a stoicheiometric amount of dilithium palladium tetrachloride[12] to obtain the (*E*)-unsaturated esters (**23**). Hydrolysis of esters (**23**) gave the acids (**24**) which, on treatment with *N*-bromosuccinimide (NBS) in aqueous potassium acetate at 60 °C, yielded the carbocyclic (*E*)-5-(2-bromovinyl)-2′-deoxyuridines (**25a** and **b**) which were separable by short-path



Scheme 4.



column chromatography (Scheme 5). The (*E*)-configuration of the bromovinyl group was confirmed by the coupling constants for the olefinic protons (*J* 16 Hz). The stereochemistry at C-1′ of the β-epimer (**25b**) was confirmed by comparison with a sample prepared *via* an unambiguous synthesis[8] and by ^{1}H n.m.r. spectral analysis.[13]



Scheme 5.

Experimental

For general experimental details see preceding paper.[5]

Benzyl N-[4β-*Dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentan*-1β-*yl*]*carbamate* (**3**).—To a solution of the acid (**1**)[5] (260 mg, 1 mmol) in dry benzene (4 ml) was added a solution of diphenylphosphoryl azide (DPPA) (275 mg, 1 mmol) in benzene (2 ml) and triethylamine (0.15 ml). The solution was gently refluxed for 90 min, a solution of benzyl alcohol (125 mg, 1.15 mmol) in benzene (1 ml) was added, and the mixture was refluxed for a further 17 h. The solution was concentrated, the residue was taken up in ether–ethyl acetate (30 ml), and the solution was washed successively with 0.5M-hydrochloric acid (10 ml), water (5 ml), and saturated aqueous sodium hydrogen carbonate (10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a light brown viscous oil, which was subjected to flash column chromatography with ether–light petroleum (3:1) as eluant. This gave the pure *urethane* (**3**) as a white solid (270 mg, 74%), m.p. 74—75.5 °C (Found: C, 62.4; H, 7.5; N, 3.75. $C_{19}H_{27}NO_6$ requires C, 62.45; H, 7.45; N, 3.83%); $\nu_{max.}$($CHCl_3$) 3 380 and 3 440 (NH), 2 830, 1 715 and 1 515 (CO_2NHR), and 1 380 and 1 370 cm^{-1}; δ_H (250 MHz; $CDCl_3$) 1.29 (3 H, s, Me), 1.48 (3 H, s, Me), 1.60 (1 H, m, 5-H_β), 2.3—2.5 (2 H, m, 4-H and 5-H_α), 3.45 (6 H, s, 2 × OMe), 4.15 (1 H, m, 1-H), 4.30 [1 H, d, C*H*$(OMe)_2$], 4.38 (1 H, br d, 2-H), 4.58 (1 H, d, 3-H), 5.12 (2 H, br s, CH_2Ph), 5.6 (1 H, br d, NH), and 7.3—7.4 (5 H, m, Ph); *m/z* 350 (M^+ − Me, 2%), 275 (4), 91 (100), and 75 (98).

N-*Benzyl*-N′-[4β-*dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentan*-1β-*yl*]*urea* (**4**).—To a solution of the acid (**1**) (260 mg, 1 mmol) in dry benzene (5 ml) was added a solution of diphenylphosphoryl azide (275 mg, 1 mmol) in benzene (2 ml) and triethylamine (0.15 ml). The solution was gently refluxed for 90 min, a solution of benzylamine (115 mg, 1.1 mmol) in benzene (2 ml) was added, and the mixture was refluxed for a further 17 h. The solution was concentrated, the residue was taken up in ether–ethyl acetate (30 ml), and the solution was washed successively with 0.5M-hydrochloric acid (10 ml), water (5 ml), and saturated aqueous sodium hydrogen carbonate (10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a brown viscous oil, which was purified by flash column chromatography with 1% methanol in ethyl acetate as eluant. This afforded the urea (**4**) as a white solid (255 mg, 70%), $\nu_{max.}$(CCl_4) 3 350 (NH), 2 830, 1 635 and 1 570 (CONH), and 1 380 and 1 370 cm^{-1}; δ_H (100 MHz; $CDCl_3$) 1.5—2.5 (3 H, m, 4-H and 5-H_2), 3.38 (3 H, s, OMe), 3.40 (3 H, s, OMe), 3.95 (1 H, m, 1-H), 4.2—4.6 (5 H, m), 5.05 (1 H, br d, NH), 5.55 (1 H, br t, N*H*CH_2), and 7.3 (5 H, m, Ph); *m/z* 349 (M^+ − Me, 4%), 333 (2), 332 (8), 231 (44), 91 (48), and 75 (100).

N-{N-[4β-*Dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentan*-1β-*yl*]*carbamoyl*}-3-*ethoxypropenamide* (**6**).—To a solution of the acid (**1**) (260 mg, 1 mmol) in dry benzene (4 ml) under nitrogen was added a solution of triethylamine (0.15 ml) and DPPA (275 mg, 1 mmol) in dry benzene (2 ml). The solution was refluxed for 75 min, cooled (ice-bath), and ammonia was bubbled through the solution for 10 min (i.r. spectroscopy showed no isocyanate remaining). The solvent was removed to give a clear viscous oil and the residue was taken up in chloroform (3.5 ml) containing pyridine (0.2 ml). (*E*)-3-Ethoxyacryloyl chloride (0.2 ml) was added, the mixture was stirred for 2 days at room temperature, and more acid chloride (0.2 ml) was added. After 24 h the solution was diluted with water (5 ml) and extracted with chloroform (15 ml). The extract was washed successively with 5% aqueous potassium hydrogen sulphate, saturated aqueous sodium hydrogen carbonate, and water and dried ($MgSO_4$). Removal of the solvent gave a brown viscous oil (~600 mg) which was subjected to flash column chromatography with 50% ether–light petroleum, followed by 5% methanol in chloroform as eluant. This gave the pure product (**6**) as a viscous oil (285 mg, 77%); $\nu_{max.}$(CCl_4) 3 240 and 3 110 (NH), 2 830, 1 680 and 1 535 (CONH), and 1 620 cm^{-1} (C=C); δ_H (250 MHz; $CDCl_3$) 1.28 (3 H, s, Me), 1.35 (3 H, t, *Me*CH_2), 1.48 (3 H, s, Me), 1.7 and 2.4 (3 H, m, 4-H and 5-H_2), 3.43 (6 H, s, 2 × OMe), 3.95 (2 H, q, OC*H*$_2$Me), 4.2—4.6 (4 H, m), 5.3 (1 H, d), 7.62 (1 H, d), 8.85 (1 H, br d, NH), and 9.44 (1 H, s, NH); *m/z* 372 (M^+, 0.2%), 357 (2), 239 (10), 99 (25), and 75 (100).

1-[4β-*Dimethoxymethyl*-2α,3α-(*isopropylidenedioxy*)*cyclopentan*-1β-*yl*]*pyrimidine*-2,4(1H,3H)-*dione* (**7**).—The enol ether (**6**) (275 mg, 0.74 mmol) was taken up in aqueous ammonia (*d* 0.88; 15 ml) and the mixture was heated under reflux for 2.5 h. The solution was concentrated, with ethanol (2 × 10 ml) as the chaser, to give a yellow solid. Flash column chromatography with 5% methanol in dichloromethane as eluant afforded the pure uracil (**7**) (170 mg, 70%) as an off-white solid (Found: M^+, 326.1422. $C_{15}H_{22}N_2O_6$ requires *M*, 326.1478); $\nu_{max.}$(CCl_4) 3 410, 3 200, and 3 060 (NH and =C–H), 2 830, and 1 695 cm^{-1} (CONH); δ_H (250 MHz; $CDCl_3$) 1.35 (3 H, s, Me), 1.5 (3 H, s, Me), 2.05 (1 H, dt, 5-H_β), 2.30 (1 H, dt, 5-H_α), 2.52 (1 H, m, 4-H), 3.48 (3 H, s, OMe), 3.40 (3 H, s, OMe), 4.38 [1 H, d, C*H*$(OMe)_2$], 4.6 (2 H, m, 1- and 3-H), 4.75 (1 H, t, 2-H), 5.75 (1 H, d, CHCO), 7.25 (1 H, d, CH=C–CO), and 8.92 (1 H, br s, NH); *m/z* 326 (M^+, 0.5%), 311 (74), 295 (11), 237 (27), 125 (36), and 75 (100).

1-[2α-*Hydroxy*-4-(*hydroxymethyl*)*cyclopent*-3-*en*-1β-*yl*]-*pyrimidine*-2,4-(1H,3H)-*dione* (**9**).—The uracil (**7**) (100 mg, 0.31 mmol) was heated under reflux in 80% acetic acid (2.5 ml) for 30 min. The solution was concentrated and azeotroped twice with benzene (10 ml). The residue (crude aldehyde) was taken up in absolute ethanol (2 ml) and water was added until the solid dissolved (few drops). After the solution had been cooled to 5 °C, sodium borohydride (50 mg, 1.3 mmol) was added and the resulting solution was stirred at room temperature for 30 min.

The solvents were removed under reduced pressure, the residue was dissolved in methanol (4 ml), and the solution was acidified with acetic acid (~0.5 ml). The solution was stirred for 30 min and the solvent was removed to give a white solid. Flash column chromatography with 30% methanol in dichloromethane as eluant afforded the pure product (**9**) as a white solid (40 mg, 57%), m.p. 185—190 °C (severe decomp.); δ_H (100 MHz; D_2O) 2.5—2.9 (2 H, m, CH_2), 4.23 (2 H, br s, CH_2OH), 4.5—4.9 (1 H, m, CHOH), 5.05 (1 H, m, CHN), 5.75 (1 H, m, CH=C), 5.86 (1 H, d, C=CH–CO), and 7.6 (1 H, d, CH=C–CO); *m/z* 206 (M^+ − H_2O, 31%), 113 (100), 112 (60), 111 (uracil, 17), and 94 (78).

Carbocyclic Uridine (**12**).—Treatment of the uracil (**7**) with Amberlite IR-150 cation-exchange resin in methanol selectively removed the isopropylidene group to give the dihydroxy acetal (**10**) which was purified by flash column chromatography with 10% methanol in dichloromethane as eluant; δ_H [100 MHz; $(CD_3)_2SO$] 3.3 (6 H, s, 2 × OMe), 4.33 [1 H, d, $CH(OMe)_2$], 5.6 (1 H, d, NCH=CH), 7.64 (1 H, d, NCHCH), and 11.1 (1 H, br s, NH); *m/z* 287 (M^+ − 1, 0.1%), 142 (10), 125 (9), 113 (12), and 75 (100).

Hydrolysis of the dimethyl acetal was accomplished as for the uracil (**17**) (*vide infra*) by heating the acetal (**10**) at 80 °C in 80% aqueous acetic acid for 15 min. This gave the aldehyde (**11**) which, on reduction with sodium borohydride in methanol–water with non-aqueous work-up,[14] gave the crude carbocyclic uridine. Flash column chromatography with 25% methanol in dichloromethane as eluant gave the pure uridine (**12**) as a white foam [yield 22% (three steps)]; δ_H (60 MHz; D_2O) 2.0—2.5 (3 H, m, CH and CH_2), 3.6 (2 H, m, CH_2OH), 3.9—4.8 (2 H, m, 2 × CHOH), 5.1 (1 H, m, CHN), 5.8 (1 H, d, C=CH–CO), and 7.65 (1 H, d, CH=C–CO); *m/z* (c.i.) 243 (M^+ + 1, 66%) and 225 (13); *m/z* 195 (1%), 193 (1), 139 (5), 130 (6), 113 (100), and 112 (17).

Benzyl N-[3β-*Dimethoxymethyl*-4α-(*methoxymethoxy*)-*cyclopentan*-1-*yl*]*carbamate* (**15**).—The reaction was carried out with the acid (**13**)[5] (248 mg, 1 mmol), by the same procedure as for the urethane (**3**). This afforded the pure urethane (**15**) as a white solid (230 mg, 65%), the n.m.r. spectrum of which suggested that it was a 1:1 epimeric mixture; $\nu_{max.}$(CCl_4) 3 440 (NH), 2 830, and 1 730 and 1 510 cm^{-1} ($NHCO_2R$); δ_H (250 MHz; $CDCl_3$) 1.4—2.5 (5 H, m, CH and 2 × CH_2), 3.3—3.4 (9 H, m, 3 × OMe), 4.0—4.3 [3 H, m, CHN, CHO, and $CH(OMe)_2$], 4.65 (2 H, m, OCH_2O), 5.1 and 5.35 (3 H, m, NH and CH_2Ph), and 7.35 (5 H, m, Ph); *m/z* 338 (M^+ − Me, 0.2%), 322 (2.4), 321 (4), 153 (49), 131 (37), 108 (36), 91 (100), and 75 (56).

N-{N-[3-*Dimethoxymethyl*-4α-(*methoxymethoxy*)*cyclo-pentan*-1-*yl*]*carbamoyl*}-3-*ethoxypropenamide* (**16**).—To a solution of the acid (**13**) (4.40 g, 17.7 mmol) and triethylamine (1.93 g, 2.67 ml, 19.2 mmol) in dry benzene (75 ml) under nitrogen was added DPPA (4.87 g, 3.81 ml, 17.7 mmol) and the solution was stirred and heated under reflux for 75 min. The solution was then cooled to *ca.* 5—10 °C and ammonia gas was bubbled through the mixture for 40 min. The solvent was removed completely under reduced pressure, the residue was taken up in chloroform (75 ml), and pyridine (3.46 g, 3.54 ml, 43.77 mmol) was added. The solution was cooled in an ice-bath, DMAP (0.25 g, catalyst) was added, followed by β-ethoxy-acryloyl chloride (3.45 ml, ~26 mmol), and the mixture was stirred at room temperature overnight. Water (50 ml) was added, the aqueous layer was extracted with chloroform (50 ml), and the combined organic layers were washed successively with 5% aqueous potassium hydrogen sulphate (50 ml, then 30 ml) and saturated aqueous sodium hydrogen carbonate (75 ml) and dried ($MgSO_4$). Concentration afforded the crude product as a brown oil which was purified by flash column chromatography (5 cm diameter column; Merck 'Kieselgel 60-Art 9385') with 2% methanol in dichloromethane as eluant. The latter provided the *title compound* as a pale yellow oil (4.2 g, 66%) (Found: C, 53.5; H, 7.8; N, 7.7. $C_{16}H_{28}N_2O_7$ requires C, 53.52; H, 7.83; N, 7.77%); $\nu_{max.}$(CCl_4) 3 240 and 3 110 (NH), 2 830, 1 680 and 1 545 (CONH), and 1 620 cm^{-1} (C=C); δ_H (250 MHz; $CDCl_3$) 1.37 (3 H, t, $MeCH_2$), 1.7—2.6 (5 H, m, CH and 2 × CH_2), 3.4 (9 H, m, 3 × OMe), 3.97 (2 H, q, OCH_2Me), 4.05—4.4 [3 H, m, CHO, CHN, and $CH(OMe)_2$], 4.65 (2 H, m, OCH_2O), 5.31 (1 H, d, C=CH–CO), 7.63 (1 H, d, C=CH–OEt), 8.67 and 8.91 (1 H, 2d, NH), and 9.08 and 9.18 (1 H, 2s, NH); *m/z* 329 (M^+ − OMe, 9%), 297 (12), 109 (30), 99 (62), and 75 (100).

1-[3β-*Dimethoxymethyl*-4α-(*methoxymethoxy*)*cyclopentan*-1-*yl*]*pyrimidine*-2,4-(1H,3H)-*dione* (**17**).—The enol ether (**16**) (2.23 g, 6.2 mmol) was refluxed in aqueous ammonia (*d* 0.88; 150 ml) for 2 h and the solvent was then removed below 40 °C under reduced pressure. The residue was partitioned between dichloro-methane (50 ml) and saturated aqueous sodium hydrogen carbonate (30 ml). The aqueous phase was extracted with dichloromethane (2 × 25 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was removed to give a brown viscous oil (1.57 g, 85%), which showed only one spot by t.l.c. (5% methanol in dichloromethane). A small amount was purified by flash column chromatography with the above eluant to give the title compound; $\nu_{max.}$(CCl_4) 3 410, 3 200, and 3 060 (NH and =C–H), 2 830, and 1 695 cm^{-1} (CONH); δ_H (250 MHz; $CDCl_3$) 1.6—2.6 (5 H, m, CH and 2 × CH_2), 3.4 (9 H, m, 3 × OMe), 4.15—4.35 [2 H, m, $CH(OMe)_2$ and CHO], 4.7 (2 H, m, OCH_2O), 5.15 (1 H, m, CHN), 5.75 (1 H, d, NCH=CH), 7.33 and 7.6 (1 H, 2d, NCH=CH), and 9.2 (1 H, br s, NH); *m/z* 283 (M^+ − OMe, 3%), 109 (27), and 75 (100).

1-[3β-*Hydroxymethyl*-4α-(*methoxymethoxy*)*cyclopentan*-1-*yl*]*pyrimidine*-2,4(1H,3H)-*dione* (**18**).—The acetal (**17**) (2.05 g 6.5 mmol) was heated in 80% aqueous acetic acid (50 ml) for 15 min at 80—85 °C. The solution was diluted with benzene (200 ml) and the benzene was removed at room temperature under reduced pressure. Toluene (200, then 100 ml) was twice added and removed at 25—30 °C under reduced pressure. The residue was taken up in dry methanol (25 ml), and ethanol (5 ml) and sodium borohydride (380 mg, 10 mmol) were added at 0 °C. The mixture was stirred for 15 min at room temperature, acetone (1 ml) was added, and the solvent was removed. The residue was dissolved in dry methanol (20 ml), and trifluoroacetic acid (~0.6 ml) was added to make the solution acidic (~pH 2). Removal of the solvent and purification of the product by flash column chromatography with 10% methanol in dichloromethane as eluant gave the pure alcohol (**18**) (1.3 g, 77%); $\nu_{max.}$(CCl_4) 3 400 and 3 200 (NH and OH) and 1 690 cm^{-1} (CONH); δ_H (100 MHz; $CDCl_3$) 1.7—2.7 (6 H, m, CH, 2 × CH_2, and OH), 3.4 (3 H, s, OMe), 3.6 (2 H, m, CH_2OH), 4.1 (1 H, m, CHO), 4.7 (2 H, s, OCH_2O), 5.3 (1 H, m, CHN), 5.75 (2 H, d, NCH=CH), 7.3 and 7.57 (1 H, 2d, NCH=CH), and 8.9 (1 H, br s, NH); *m/z* 270 (M^+, 3%), 225 (9), 167 (15), 113 (69), 96 (37), and 45 (100).

1-[3α-*Hydroxy*-4β-(*hydroxymethyl*)*cyclopentan*-1-*yl*]-*pyrimidine*-2,4(1H,3H)-*dione* (**19**).—A solution of the protected carbocyclic deoxyuridine (**18**) (1.3 g, 4.8 mmol) in methanol (30 ml) containing concentrated hydrochloric acid (0.5 ml) was refluxed for 25 min. The solution was neutralized with 2M-sodium hydroxide followed by saturated aqueous sodium hydrogen carbonate and the solvent was removed below 40 °C under reduced pressure. Ethanol (30 ml) was twice added and removed. The residue was taken up in ethanol (3 × 20 ml), and the solution was filtered and concentrated. Flash column chromatography with 20% methanol in dichloromethane as eluant gave the pure carbocyclic 2′-deoxyuridine (**19**) as an

epimeric mixture (700 mg, 62%). The two epimers were separated by short-path column chromatography (Merck 7729) with 10—15% methanol in dichloromethane as gradient eluant: $\lambda_{max.}(H_2O)$ 269 (ε 9 700); (0.1M-HCl) 269 (9 200); (0.1M-NaOH) 266 nm (7 300); $\nu_{max.}$(Nujol) 1 700 cm^{-1} (uracil); δ_H (250 MHz; D_2O) (α-epimer) 1.88 (1 H, ddd, 2-H_α), 2.0 (1H, m, 5-H_β), 2.1 (1 H, m 5-H_α), 2.3 (1H, m, 4-H), 2.5 (a H, ddd, 2-H_β), 3.65 (2 H, 2dd, CH_2OH), 4.11 (1 H, q, 3-H), 4.9 (1 H, m, 1-H), 5.9 (1 H, d, NCH=C*H*), and 7.86 (1 H, d, NC*H*=CH); δ_H (250 MHz; D_2O) (β-epimer) 1.59 (1 H, dt, 5-H_β), 2.1 (2 H, m, 2-H_2 and 4-H), 2.36 (1 H, dt, 5-H_α), 3.7 (2 H, 2ddd, CH_2OH), 4.24 (1 H, q, 3-H), 5.02 (1 H, m, 1-H), 5.87 (1 H, d, NCH=C*H*), and 7.73 (1 H, d, NC*H*=CH); *m/z* 226 (M^+, 20%), 208 (4), 167 (31), 139 (24), 113 (98), 112 (24), and 96 (100).

Chloro-{1,2,3,4-tetrahydro-1-[3α-hydroxy-4β-(hydroxymethyl)cyclopentan-1-yl]-2,4-dioxopyrimidin-5-yl}mercury (**22**).—To a solution of the carbocyclic 2′-deoxyuridine (**19**) (1.0 g, 4.42 mmol) in water (4 ml) was added a solution of mercury(II) acetate (1.48 g, 4.64 mmol) in water (6.5 ml). To this solution was added further water (3.5 ml) and the mixture was stirred and heated at an internal temperature of 50 °C for 3 h during which time a thick white precipitate developed. Aqueous sodium chloride (0.64 g, 10.95 mmol in 2 ml) was then added at 40 °C and the mixture was stirred to room temperature and then cooled in ice. The precipitated product was filtered off and washed successively with 0.1M-NaCl (8 ml), water (5 ml), and ethanol (3 ml). The resulting solid was dried *in vacuo* at 60 °C over P_2O_5 to yield the title compound (1.15 g, 65%). This material was used directly in the next stage.

Ethyl (E)-3-*{1,2,3,4-Tetrahydro-1-[3α-hydroxy-4β-(hydroxymethyl)cyclopentan-1-yl]-2,4-dioxopyrimidin-5-yl}propenoate* (**23**).—The carbocyclic 5-chloromercury-2′-deoxyuridine (**22**) (390 mg, 0.87 mmol), ethyl acrylate (0.75 ml) and dilithium palladium tetrachloride in methanol (0.1M solution; 8.7 ml, 0.87 mmol) were stirred together for 16 h under nitrogen. The solution was filtered, the precipitate was washed with warm methanol (20 ml), and then hydrogen sulphide gas was bubbled through the combined methanol solutions to precipitate brown mercury sulphide. The solution was filtered through Hyflo, the solvent was removed, and water (5 ml) was added and then removed at 30 °C under reduced pressure. Flash column chromatography of the residue with 15—20% ethanol in chloroform as gradient eluant gave the unsaturated ester (**23**) (195 mg, 69%) (Found: M^+, 324.1385. $C_{15}H_{20}N_2O_6$ requires *M*, 324.1321); δ_H [250 MHz; $(CD_3)_2SO$] 1.24 (3 H, t, *Me*CH_2), 1.4—2.3 (5 H, m, CH and 2 × CH_2), 3.5 (2 H, m, CH_2OH), 3.95 and 4.05 (1 H, 2m, C*H*OH), 4.16 (2 H, q, OCH_2Me), 4.88 and 5.00 (1 H, 2m, CHN), 6.86 and 6.92 (1 H, 2d, *J* 16 Hz, CH=C*H*CO_2), 7.4 and 7.44 (1 H, 2d, C*H*=CHCO_2), and 8.31 and 8.43 (1 H, 2s, NC*H*=C); *m/z* 324 (M^+, 14%), 295 (8), 279 (7), 165 (54), and 137 (100).

(E)-3-*{1,2,3,4-Tetrahydro-1-[3α-hydroxy-4β-(hydroxymethyl)cyclopentan-1-yl]-2,4-dioxopyrimidin-5-yl}propenoic Acid* (**24**).—The ester (**23**) (180 mg, 0.56 mmol) was stirred in 0.5M-aqueous sodium hydroxide (2.5 ml, 1.25 mmol) at room temperature for 4 h. Dowex 50G-X8 cation-exchange resin was added (to pH 4). The solution was filtered and the solvent was removed at 30—35 °C under reduced pressure to give the acid as an off-white solid (131 mg, 80%) (Found: M^+, 296.101. $C_{13}H_{16}N_2O_6$ requires *M*, 296.1008); $\nu_{max.}$(Nujol) 1 700 cm^{-1} region (CO_2H and uracil); δ_H [250 MHz; $(CD_3)_2SO$] 1.4—2.3 (5 H, m, CH and 2 × CH_2), 3.6 (2 H, m, CH_2OH), 3.95 and 4.05 (1 H, 2m, C*H*OH), 4.95 and 5.05 (1 H, 2m, CHN), 6.70 and 6.77 (1 H, 2d, CH=C*H*CO_2), 7.14 and 7.2 (1 H, 2d, C*H*=CHCO_2), and 8.13 and 8.31 (1 H, 2s, NCH=C); *m/z* 296 (M^+, 1%), 252 (4), 177 (12), 138 (15), and 44 (100).

(E)-5-(2-*Bromovinyl*)-[3α-*hydroxy*-4β-(*hydroxymethyl*)-*cyclopentan*-1-*yl*]*pyrimidine*-2,4(1H,3H)-*dione* (**25**).—The acid (**24**) (0.45 g, 1.52 mmol) and potassium acetate (0.32 g, 3.20 mmol) were stirred in water (20 ml) at 60—65 °C until a clear solution was obtained (*ca.* 10 min). NBS (0.28 g, 1.60 mmol) was then added in small portions during 15 min, the mixture then being stirred at 60—65 °C for 10 min and at room temperature for 2 h. The mixture was evaporated to dryness under reduced pressure at 35 °C, the residue was taken up in methanol (*ca.* 50 ml), and the solution was evaporated onto silica ('Kieselgel 60–Art 9385,' *ca.* 15 g). The impregnated material was applied to a flash chromatography column (4.5 cm diameter); elution with 10% methanol in dichloromethane provided the title compound as a mixture of epimers (0.22 g, 44%).

The epimers were separated as follows. The preceding epimeric mixture (155 mg) was dissolved in warm methanol (*ca.* 20 ml) and the solution was evaporated onto silica (5 g, Merck 'Kieselgel 60–Art 7734'). The impregnated material was carefully applied to 'short-path' column (30 g, Merck 'Kieselgel 60–Art 7729'). Elution with 10% ethanol in chloroform provided initially the pure α-epimer (**25a**) (42 mg), m.p. 157—160 °C (decomp.), then a mixture enriched in the β-epimer (**25b**) (75 mg). This mixture was then chromatographed as above, yielding further pure α-epimer (12 mg) and then the desired β-epimer as a white powder (32 mg, 6.4%), m.p. 181—183 °C (decomp.) [Found: M^+, 330.0207. $C_{12}H_{15}N_2O_4Br^{79}$ requires *M*, 330.0218; Found: $M^+ + 2$, 332.0191. $C_{12}H_{15}N_2O_4Br^{81}$ requires *m/z* 332.0198 ($M + 2$)]; δ_H (250 MHz; CD_3OD)(α-epimer) 1.84 (1 H, ddd, 2-H_α), 2.06 (2 H, m, 5-H_2), 2.28 (1 H, m, 4-H), 2.43 (1 H, ddd, 2-H_β), 3.6 (2 H, m, CH_2OH), 4.1 (1 H, q, 3-H), 5.0 (1 H, m, 1-H), 6.83 (1 H, d, *J* 14 Hz, CH=C*H*Br), 7.35 (1 H, d, C*H*=CHBr), and 7.95 (1 H, s, NCH=C); δ_H (250 MHz; CD_3OD) (β-epimer) 1.6 (1 H, dt, 5-H_β), 2.05 (3 H, m, 4-H and 2-H_2), 2.28 (1 H, ddd, 5-H_α), 3.7 (2 H, m, CH_2OH), 4.19 (1 H, m, 3-H), 5.07 (1 H, m, 1-H), 6.81 (1 H, d, *J* 14 Hz, CH=C*H*Br), 7.34 (1 H, d, C*H*=CHBr), and 7.76 (1 H, s, NCH=C); *m/z* 332 ($M^+ + 2$, 1%), 330 (M^+, 1), 251 (42), and 137 (100).

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