Carbohydrate Research, 85 (1980) 15–32
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SYNTHESIS OF 6-SUBSTITUTED URIDINES. SYNTHESIS OF (*R* or *S*)-6-(3-AMINO-2-CARBOXYPROPYL)URIDINE

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(Received September 5th, 1979; accepted for publication in revised form, November 15th, 1979)

ABSTRACT

Addition of 5-bromo-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (**2**) in pyridine to an excess of 2-lithio-1,3-dithiane (**3**) in oxolane at −78° gave (6*R*)-5,6-dihydro-(1,3-dithian-2-yl)-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (**4**), (5*S*,6*S*)-5-bromo-5,6-dihydro-(1,3-dithian-2-yl)-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (**5**), and its (5*R*) isomer **6** in yields of 37, 35, and 10%, respectively. The structure of **4** was proved by Raney nickel desulphurization to (6*S*)-5,6-dihydro-2′,3′-*O*-isopropylidene-6-methyl-5′-*O*-trityluridine (**7**) and by acid hydrolysis to give D-ribose and (6*R*)-5,6-dihydro-6-(1,3-dithian-2-yl)uracil (**9**). Treatment of **4** with methyl iodide in aqueous acetone gave a 30% yield of (*R*,*S*)-5,6-dihydro-6-formyl-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (**10**), characterized as its semicarbazone **11**. Both **5** and **6** gave **4** upon brief treatment with Raney nickel. Both **5** and **6** also gave 6-formyl-2′,3′-*O*-isopropylidene-5′- *O*-trityluridine (**12**) in ~41% yield when treated with methyl iodide in aqueous acetone containing 10% dimethyl sulfoxide. A by-product, identified as the *N*-methyl derivative (**13**) of **12** was also formed in yields which varied with the amount of dimethyl sulfoxide used. Reduction of **12** with sodium borohydride, followed by deprotection, afforded 6-(hydroxymethyl)uridine (**17**), characterized by hydrolysis to the known 6-(hydroxymethyl)uracil (**18**). Knoevenagel condensation of a mixture of the aldehydes **12** and **13** with ethyl cyanoacetate yielded 38% of *E*- (or *Z*-)6-[(2-cyano-2-ethoxycarbonyl)ethylidene]-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (**19**) and 10% of its *N*-methyl derivative **20**. Hydrogenation of **19** over platinum oxide in acetic anhydride followed by deprotection gave *R* (or *S*)-6-(3-amino-2-carboxypropyl)uridine (**23**).

INTRODUCTION

The introduction of *C*-linked substituents at C-6 of pyrimidine nucleosides has not, until lately, received a great deal of attention, despite the knowledge that nucleosides substituted at C-5 or on the sugar moiety display a wide range of biological activities[1–6]. Part of the reason for this lack stems from problems of synthesis; the direct condensation of such 6-substituted pyrimidines as 6-methyluracil[7–9] and orotic acid[10] with suitable sugar derivatives generally leads to the formation of

0008-6215/80/0000–0000/S 02.25,

mixtures of N-3 and N-1 nucleosides, presumably owing to steric hindrance by the C-6 substituent. Thus, modification at C-6 has been best pursued by working on the pre-formed nucleosides. For instance, simple alkyl groups have been introduced at C-6 of uridine by Claisen rearrangement of 5-allyloxyuridine to give 6-allyl-5-hydroxyuridine[11] and, more recently, by photolytic addition of alcohols to uridine to give 5,6-dihydro-6-hydroxyalkyluridines[12] which, after mesylation of the free hydroxyl group and treatment with sodium hydride, gave 6-alkyluridines[13] in reasonable yields. Less-direct routes to 6-alkyluridines[14] and 6-alkyl-O^2,2'-anhydro-5,6-dihydrouridines[15] have employed reactions of 3-substituted α,β-unsaturated esters with pentose 2-amino-1',2'-oxazoline derivatives.

A previous report[16] from this laboratory described the Michael-type 1,4-addition of the anion of 1,3-dithiane[17] to C-6 of O^2,2'-anhydrouridine to give, among other products, the novel 6(*S*)-1-β-D-arabinofuranosyl-5,6-dihydro-6-(1,3-dithian-2-yl)uracil. Our work on synthesis of aminoacyl branched-chain nucleosides[18-22], analogues of the biologically important polyoxins, provided a method of extending such studies to the C-6 position of pyrimidine nucleosides *via* the formyl functionality accessible from the 1,3-dithiane group. Klein and Fox[23] used a similar approach to the elaboration of a polyfunctional chain branch at C-6 by employing a Wittig reaction with 2',3',5'-tri-*O*-acetyl-6-formyluridine. Synthesis of the latter compound, however, proceeded from a poor-yielding, multi-step preparation of 6-methyluridine. Synthesis of a 6-formyluridine derivative from our dithiane addition-product would have required the unprecedented dehydrogenation of the 6-substituted 5,6-dihydro linkage[24]. A fairly recent report by Ueda[25] described the Michael-type 1,4-addition of cyanide anion to C-6 of 5-bromouridine with concomitant dehydrobromination to give 6-cyanouridine. It thus seemed reasonable that the dithiane anion, which had already demonstrated a tendency to attack pyrimidine anhydronucleosides at C-6, would behave likewise with 5-bromouridine and that furthermore, a dehydrobromination process similar to that observed by Ueda would generate the desired 5,6-double bond. We thus present in this paper a convenient synthesis of 6-formyluridine through the reaction of 2-lithio-1,3-dithiane with protected 5-bromouridine, and utilization of this aldehyde to attach a β-amino acid at C-6.

RESULTS AND DISCUSSION

Although Ueda[25], used a 5'-*O*-acetyl derivative of 5-bromouridine in his study of its reaction of potassium cyanide, a base-labile blocking group was avoided in the present work. Thus, 5-bromo-2',3'-*O*-isopropylidene-5'-*O*-trityluridine (**2**) was prepared by tritylation of the known isopropylidene derivative[26] **1** by using standard procedures[27]. A solution of **2** in anhydrous pyridine was then added at −78° under dry nitrogen to a six-fold molar excess of the dithiane anion[17] **3** in oxolane. After 24 h at −20°, three dithiane addition-products, **4**, **5**, and **6**, were isolated chromatographically in yields of 37, 35, and 10%, respectively.

Neither the elemental analysis nor the mass spectrum of **4** showed presence of

bromine, but simple nucleophilic displacement of the bromide of **2** by the dithiane anion was precluded by the absence in the n.m.r. spectrum of **4** of a low-field singlet for H-6; a two-proton multiplet at δ 2.48–2.71 ($CDCl_3$) suggested a 5,6-dihydro structure. In order to simplify the spectrum, compound **4** was desulfurized with Raney nickel to give the 6-methyl derivative **7**. The n.m.r. spectrum of **7** in $CDCl_3$ showed an ABX pattern for H-5a, H-5e, and H-6, the chemical shifts and coupling constants of which were characteristic of a 6-substituted 5,6-dihydro system[28]. The methyl group gave rise to a doublet at δ 1.36. Further proof of structure of **4** came from its deprotection in hot acetic acid to yield (6*R*)-5,6-dihydro-6-(1,3-dithian-2-yl)uridine (**8**). The u.v. spectrum of **8** in methanol showed a weak absorption at 245 nm for the dithiane moiety[29] but none arising from uracil, indicating that saturation of the 5,6-double bond had indeed occurred. When compound **8** was heated for 4 h at 80° in M hydrochloric acid, white needles of the free base **9** formed upon cooling the mixture. Compound **9** was identical by m.p. and n.m.r. spectrum (6*S*)-5,6-dihydro-6-(1,3-dithian-2-yl)uracil previously prepared in our laboratory[16]. Significantly, however, the latter compound had an optical rotation of opposite sign to that of **9**, so that these two compounds appear to be enantiomers. Moreover, comparison of the c.d. spectra of their precursors [namely, **8** and (6*S*)-5,6-dihydro-6-(1,3-dithian-2-yl)-1-β-D-arabinofuranosyluracil][16] also showed that, while the latter displayed a positive Cotton effect at 250 nm, compound **8** showed a definite negative effect at the same wavelength. Thus, it may be concluded that compounds **4**, **8**, and **9** have the *R* configuration about C-6.

The formation of compound **4** from **2** may be explained by assuming an initial vinyl halogen–metal exchange between **2** and the anion **3** to give the protected 5-lithiouridine. It has been shown that, in the presence of butyllithium, 5-bromouracil and its nucleosides exist in equilibrium with their 5-lithio derivatives[30,31]. A Michael-type 1,4-addition at C-6 of another dithiane anion (which is in excess) would then give, after quenching, the 5,6-dihydro-6-dithianyl species* **4**. The apparent stereoselectivity of the addition may be rationalized by assuming that the pyridimine moiety of compound **2** (and its 5-lithio derivative) adopts the more-stable *anti* orientation with respect to the plane of the furanose ring[32–34], so that *endo* attack by the dithiane anion at C-6 is impeded by the bulky trityl group, whereas *exo* attack, with formation of the *R* isomer, is favored. Such steric controls to the direction of addition of reagents at C-6 of pyrimidine nucleosides by the 5′-*O*-trityl group have been observed[13].

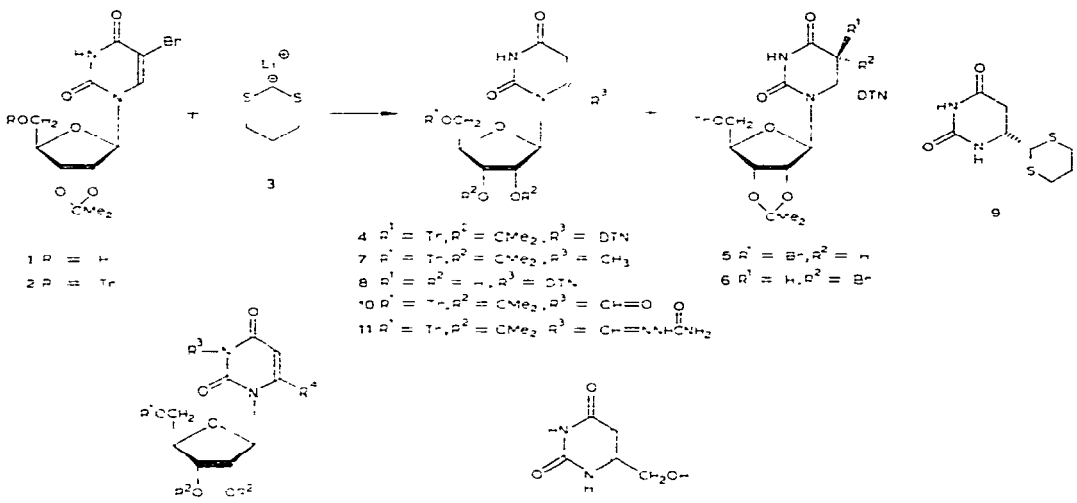
Formation of the 5,6-dihydro-6-formyl nucleoside **10** by alkylative hydrolysis of the dithiane moiety of **4** with methyl iodide and barium carbonate in aqueous acetone[35] proceeded smoothly. Compound **10** was characterized as its semicarbazone **11** by i.r., n.m.r., and elemental analysis. Isomerization of the aldehyde group of **10** about C-6 owing to the acidity of H-6 and the basic hydrolytic conditions exployed is not to be discounted. This possibility would perhaps explain the lack of resolution

*One referee suggested that **4** may be the product of lithiation of **5** or **6**, or **4** may arise by reduction of **5**, **6**, in the presence of free thiol impurities.

observed in the signals of the n.m.r. spectrum of the derived semicarbazone **11**.

That compounds **5** and **6**, the other two products isolated from the reaction of **2** with **3**, bore a diastereomeric relationship, was initially indicated by their chromatographic properties. Whereas the mixture had shown, by t.l.c. on silica gel, a preponderance of compound **6** with respect to **5**, it was found that, after chromatography on silica gel, compound **5** was now the major product with respect to **6**. As anticipated, both **5** and **6** contained bromine. However, although analysis of compound **5** indicated the formula $C_{35}H_{37}BrN_2O_6S_2$, that of **6** did not show a complete mole of bromine, perhaps because of partial elimination of HBr during drying of the analytical sample *in vacuo* at elevated temperature. The high-resolution mass spectrum of **6** showed an $M^+ - CH_3$ peak at 711.1027 corresponding to $C_{34}H_{34}{}^{81}BrN_2O_6S_2$.

Brief treatment of compounds **5** and **6** with Raney nickel in boiling ethanol gave the dehalogenated product **4**, identical by R_F value: n.m.r. spectrum mass, spectrometry and, most importantly, optical rotation with that of the compound obtained directly from the reaction of **2** with the dithiane anion **3**, the configuration at C-6 of which has been shown already to be *R*. Thus **5** and **6** must differ only in their configurations at C-5, and the latter were established by comparing the coupling constants of H-5 and H-6 ($J_{5,6}$) observed in the n.m.r. spectra of these two com-



pounds in chloroform-*d*. For compound **5**, H-5 gave a doublet at δ 5.12, $J_{5,6}$ 1.6 Hz, whereas H-5 of compound **6** was at slightly higher field (δ 4.80) and had a significantly larger $J_{5,6}$ value (6.0 Hz). As 5,6-dihydrouracil (and its 5,6-substituted derivatives) exists mainly in a half-chair conformation[36-39] and, furthermore, *cis* hydrogen atoms at these positions give rise to coupling constants ($J_{a,e}$) ranging from 5.2 to 7.23 Hz[28c,39], it was then inferred that **6** was the *cis* isomer. Compound **5** was thus the 5,6-*trans* isomer. The latter assignment is also consistent with the observed coupling-constant ($J_{e,e}$) of H-5 and H-6 in this compound, if it is assumed that the bulky bromo and dithiane substituents adopt a 5,6-diaxial relationship[37,39] so that H-5 and H-6 are diequatorial. *trans*-Diequatorial 5,6-protons were observed to have $J_{5e,6e}$ 2.5 Hz in 5-bromo-2'-deoxy-5,6-dihydro-6-hydroxyuridine[28b,40]. Thus, as the configuration of the dithiane moiety of **5** and **6** was determined here to be 6*R*, then **5** must have the 5*S*,6*S* configuration (namely, *trans*) and **6** the 5*R*,6*S* geometry (*cis*).

This stereochemical assignment is consistent with the observed instability of **6** on silica gel; this acidic medium catalyzes isomerization to the thermodynamically more stable 5,6-*trans* compound (**5**), presumably *via* enolization of the C-4 carbonyl group. The *cis* isomer **6** may thus be considered as the kinetically favored 1,4-addition product of **2** and **3**. Whereas the reaction of cyanide ion with 5-bromouridine gave a similar Michael-type of 1,4-addition product, which spontaneously dehydrobrominated to regenerate the 5,6 double bond[25], no such elimination was observed in this example of 1,3-dithiane addition. This difference may be attributed to the much greater electronegativity of the cyanide group as compared to the dithiane group, with the resulting increase in the acidity of H-6 and consequent ease of elimination. It was therefore to be expected that conversion of the thioacetal group of **5** or **6**, by methyl iodide and barium carbonate in aqueous acetone, into the (more electronegative) formyl functionality, should result in concomitant elimination of HBr to give the blocked "orotidine aldehyde" **12**. The n.m.r. spectrum of the crude product in chloroform-*d* showed a singlet for the formyl proton at δ 9.53, the same position reported by Klein and Fox[23] for the formyl proton of 2',3',5'-tri-*O*-acetyl-6-formyluridine. As these authors also stated that the last-named compound was unstable, compound **12** was characterized as its semicarbazone **14**. The n.m.r. spectrum of **14** in dimethyl sulfoxide-d_6 displayed, in addition to four D_2O-exchangeable protons, a singlet for H-5 at δ 5.96 (superposed on H-1', also a singlet) as well as a sharp singlet at δ 7.56 attributed to the imino proton. This evidence, together with the elemental analysis and mass spectrum, provided convincing proof that hydrogen bromide had been eliminated from **5** to give **12** and thence **14**.

If the alkylative hydrolysis of **5** to the aldehyde **12** was conducted in 10% aqueous acetone at 55°, only partial hydrolysis was observed by t.l.c., even after seven days of reaction. When 10% by volume of dimethyl sulfoxide was included in the mixture, complete hydrolysis was accomplished within four days at 55°. However, in addition to the 6-aldehyde **12**, a minor compound of higher R_F value was also formed and was shown to be the N-3 methylated 6-aldehyde **13**, also characterized as its semicarbazone, **15**. The n.m.r. spectrum of **15** showed only three D_2O-exchange-

able protons, but displayed a three-proton singlet at δ 2.98 for the *N*-methyl group. Furthermore, the mass spectrum of **15** indicated a mass of 14 units greater than the un-methylated derivative **14**. Both the rate of hydrolysis and the amount of *N*-methylated product **13** and side-products increased with increasing concentration of dimethyl sulfoxide until, if only 10% aqueous dimethyl sulfoxide was used as the solvent, all starting nucleoside had disappeared within 30 min with, however, little formation of **12**. The *N*-methylation of pyrimidines and purines with methyl iodide under basic conditions has been reported[41].

When the *cis* 5-bromo-6-dithianyl dihydronucleoside **6** was subjected to alkylative hydrolysis with methyl iodide, and semicarbazones formed of the products, compounds **14** and **15** were isolated, identical in all respects with the semicarbazones derived from **5**. This result provided further proof that compounds **5** and **6** are configurational isomers about C-5 and C-6.

Reduction of the 6-aldehyde **12** with sodium borohydride in ethanol gave 6-(hydroxymethyl)-2′,3′-*O*-isopropylidene-5′-*O*-trityluridine (**16**) in 72% yield from **5**. The n.m.r. spectrum of **16** in $CDCl_3$ showed signals for a D_2O-exchangeable hydroxyl proton at δ 1.54, the N-3 proton at δ 8.06, and the methylene group as a singlet at δ 4.58. Addition of D_2O changed the latter to a doublet (J_{gem} 6.4 Hz). The i.r. spectrum of **16** in chloroform solution showed a sharp N–H absorption at 3420 cm^{-1} superposed on a broad O–H band. Compound **16** was boiled under reflux in 80% aqueous acetic acid for 25 min to give 6-(hydroxymethyl)uridine (**17**) as a clear syrup after chromatographic purification. The n.m.r. spectrum of **17** in dimethyl sulfoxide-d_6 was completely consistent with the assigned structure, showing a total of five, D_2O-exchangeable protons. The C-6 methylene-group signal was observed as a singlet. The u.v. spectrum of **17** in methanol exhibited a maximum at 258 nm. Although Ueda[42] has reported a m.p. for 5′-*O*-acetyl-6-(hydroxymethyl)-2′,3′-*O*-isopropylideneuridine, no other physical constants for 6-(hydroxymethyl)-uridine or its derivatives were found in the literature. Accordingly, in order to confirm the structural assignment, compound **17** was subjected to acid hydrolysis with M hydrochloric acid for 12 h at 90°, to give the known[43–45] 6-hydroxymethyluracil (**18**).

As our ultimate synthetic goal was 6-(aminoacyl) carbon–carbon branched-chain pyrimidine nucleosides, application of the Knoevenagel condensation of ethyl cyanoacetate with the 6-formyluridine derivative **12** seemed appropriate. This reaction has previously been employed in our laboratory[46] to make branched-chain sugars from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 2,5-anhydro-3,4,6-tri-*O*-benzoyl-D-allose. A solution of the crude aldehyde, consisting of a mixture of **12** and **13**, and ethyl cyanoacetate in anhydrous *N*,*N*-dimethylformamide was stirred for 2 h at room temperature in the presence of a catalytic amount of ammonium acetate as base, to give two products, **19** and **20**, isolated by chromatography in yields of 38 and 10%, respectively. The n.m.r. spectra of both products in $CDCl_3$ were essentially identical, showing the ethyl ester signals as a sharp triplet (CH_3) and quartet (CH_2) near δ 1.40 and 4.40, respectively, together with a low-field (δ 8.1)

singlet for the chain-branch vinyl proton. However, whereas **19** showed a broad, low-field, D_2O-exchangeable signal for the N-3 proton, no such signal was seen in the spectrum of **20**. Instead, a sharp, 3-proton singlet at δ 3.14 indicated that **20** was the 3-*N*-methyl derivative. The i.r. spectrum of **20** in carbon tetrachloride substantiated the absence of the NH group and moreover, displayed three carbonyl signals at 1745, 1725, and 1680 cm^{-1} which served as proof that **20**, as well as the precursor **13** and the semicarbazone **15**, were *N*-methylated rather than *O*-methylated.

The lack of multiplicity of the signals in the n.m.r. spectra of **19** and **20** was taken as evidence that only one of the possible *E* and *Z* isomers had been formed in each instance. Klein and Fox[23] also observed formation of only the *trans* isomer of 3-(6-uridinyl)acrylic acid ethyl ester in the reaction of ethoxycarboxylmethylenetriphenylphosphorane with protected 6-formyluridine in *N*,*N*-dimethylformamide. Moreover, it has been demonstrated[47,48] that ethyl cyanoacetate generally condenses stereoselectively with aldehydes to give the isomer in which the two bulkiest groups are *trans*. Accordingly, for both compounds **19** and **20**, the isomer in which the carboxyethyl and nucleoside moiety are *trans* would be favored. No attempt was made to verify this assignment, as hydrogenation of the nitrile group of **19** or **20** to the corresponding amine would also be expected to saturate the exocyclic double-bond of these compounds and thus remove the center of geometrical isomerism. This was, in fact, accomplished for **19** by using platinum oxide as catalyst and acetic anhydride as solvent to give, after 20 h at 50 $lb.in.^{-2}$ of hydrogen, the *N*-acetyl derivative **21**. Although **21** gave an acceptable analysis for $C_{39}H_{43}N_3O_9$, the mass spectrum showed, in addition to the molecular-ion peak at *m/e* 697, several peaks for higher mass centered at *m/e* 709, indicating that partial reduction of the trityl group had occurred. This was confirmed by the n.m.r. spectrum of **21** in chloroform-*d*, which showed a very complex pattern of high-field signals arising from the reduced phenyl rings. However, from the n.m.r. spectrum of **21**, it could still be concluded that (*a*) the signal of the exocyclic vinylic proton, observed at δ 8.1 in the n.m.r. spectrum of the unreduced compound **19**, was no longer present and thus the exocyclic double-bond had become saturated, (*b*) the nitrile group was converted into the *N*-acetamide, as shown by the appearance of an additional, D_2O-exchangeable N–H signal and a sharp singlet at δ 1.95, and (*c*) the pyrimidine ring of **21** had not been reduced, as H-5 gave a sharp singlet at δ 5.64. Selective reduction of unsaturated side-chains of pyrimidine nucleosides is not uncommon[49].

When compound **21** was partially deprotected with trifluoroacetic acid, the resulting product (**22**) appeared to be a single isomer, as shown by the lack of multiplicity in the signals of its n.m.r. spectrum (Me_2SO-d_6). Although catalytic hydrogenation generally causes *cis*-hydrogenation at the least-hindered face of a double bond[50], molecular models did not permit unequivocal prediction of the geometry that might be expected in compound **22**. The u.v. spectrum of **22** in methanol displayed a strong absorption at 260 nm, additional proof that the 5,6-double bond was not reduced during the hydrogenation of compound **19**. The c.d. spectrum of nucleoside **22** in water showed an extremely weak Cotton effect in the 260-nm region. This result is

consistent with the observation that 6-substituted pyrimidine nucleosides having the β-configuration adopt the *syn* conformation[51].

When, in an attempt to remove the protecting groups of the amino acid moiety, a solution of **22** in concentrated barium hydroxide was boiled for 4–10 h under reflux, the organic material isolated did not have an n.m.r. spectrum consistent with that expected for the completely deprotected nucleoside. In particular, no anomeric-proton signal was observed. To avoid this excessively vigorous deprotection step, compound **19** was hydrogenated in the absence of acetic anhydride. The reaction gave, in reasonable yield, the free amine **23**, as indicated by i.r. and n.m.r. spectroscopy. Deprotection of **23** now proceeded smoothly under mild conditions: treatment of **23** with trifluoroacetic acid at room temperature removed the protecting groups of the sugar moiety and the ester group was removed by using methanolic sodium methoxide and water, also at room temperature. The product, *R* (or *S*)-6-(3-amino-2-carboxypropyl)uridine (**24**), showed the H-1′ and H-5 signals as singlets in the n.m.r. spectrum.

The β-alanyl nucleoside **24** is a structural isomer of N^3-(3-L-amino-3-carboxypropyl)uridine, a nucleoside found[52] at position 47 in the extra loop of *E. coli t*-RNA and synthesized by Seela and Cramer[53].

EXPERIMENTAL

General. — ^{1}H-N.m.r. spectra were determined in chloroform-*d* or dimethyl sulfoxide-d_6 with tetramethylsilane as the standard (set at $\delta = 0$) by using a Varian XL-100 spectrometer. Values given for coupling constants are first order. Optical rotations were measured at room temperature with a Perkin–Elmer Model 141 automatic polarimeter. The c.d. measurements were performed with a Jasco J-20 automatic recording spectropolarimeter at room temperature, and i.r. spectra with a Perkin–Elmer 727B spectrometer. Melting points are corrected and were measured with a Leitz microscope heating-stage, Model 350. Solutions were dried with sodium sulfate and evaporated under diminished pressure. Mass spectra were determined with a HMS-9 spectrometer. Column chromatography was performed with t.l.c.-grade Silica Gel H without binder (Merck) under a pressure of 4–8 lb.in^{-2} and flow rates of 70–140 mL.h^{-1}, and t.l.c. with Silica Gel G was used to monitor all reactions. Chemical analyses were performed by Mr. P. Borda of the Microanalytical Laboratory of the University of British Columbia.

5-Bromo-1-(2,3-O-isopropylidene-5-O-trityl-β-D-ribofuranosyl)uracil (**2**). — A solution of 5-bromo-2′,3′-*O*-isopropylideneuridine (**1**; 7.8 g, 21.5 mmol) and freshly recrystallized chlorotriphenylmethane (6.14 g, 22 mol) in anhydrous pyridine (150 mL) was heated for 4 h at 100°. The mixture was then cooled and poured into rapidly stirred water (1200 mL). The water layer was decanted and the remaining gum dissolved in chloroform (1 L) and the solution washed with water (2 × 250 mL). The organic layer was dried and evaporated, and the residue crystallized from ether–hexane to give **2** as colourless needles (12.5 g, 96%), m.p. 201–202.5°, $[\alpha]_D^{23}$ −25.5°

(*c* 1.1, chloroform); n.m.r. (100 MHz, $CDCl_3$): δ 1.31 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 3.40 (d, 2 H, $J_{4',5'}$ 3.6 Hz, H-5'), 4.33 (q, 1 H, $J_{3',4'}$ 7.0 Hz, H-4'), 4.73 (dd, 1 H, $J_{2',3'}$ 3.0 Hz, H-3'), 4.86 (dd, 1 H, $J_{1',2'}$ 2.4 Hz, H-2'), 5.87 (d, 1 H, H-1'), 7.18–7.50 (m, 15 H, Ar), 7.86 (s, 1 H, H-6), and 9.06 (broad s, 1 H, N*H*, exchangeable with D_2O): *m/e* 606 (M^+ for ^{81}Br), 604 (M^+ for ^{79}Br).

Anal. Calc. for $C_{31}H_{29}BrN_2O_6$: C, 61.50; H, 4.79; N, 4.63. Found: C, 61.57; H, 4.59; N, 4.90.

Synthesis of (6R)-*5,6-dihydro-6-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine* (**4**), (5S,6S)-*5-bromo-5,6-dihydro-6-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine* (**5**), *and* (5R,6S)-*5-bromo-5,6-dihydro-6-(1,3-dithian-2-yl)-2',3'-O-isopropylidene-5'-O-trityluridine* (**6**). — To a solution of 1,3-dithiane (6.90 g, 57.6 mmol) (dried by azeotroping with benzene) in dry oxolane (tetrahydrofuran, THF) (150 mL) was added butyllithium in hexane (34.2 mL of a 1.6M solution) under nitrogen at −78°. The pale-yellow solution was stirred for 30 min and then warmed to −20° and stirred for an additional 4 h. The solution was then cooled again to −78° and a solution of nucleoside **2** (5.56 g, 9.2 mmol) in anhydrous pyridine (50 mL) was added dropwise during 45 min, whereupon the deep-red mixture was stored for 24 h at −20°. The solution was then poured into a rapidly stirred mixture of ether and saturated aqueous sodium chloride (800 and 100 mL, respectively), the aqueous layer drawn off, and the organic layer washed to neutrality with saturated salt solution. The organic layer was dried and evaporated to a syrup that was chromatographed on silica gel (500 g) with 10:1 benzene–ethyl acetate as developer, to yield compound **5** as a foam (2.3 g, 35%), which was crystallized from methanol: m.p. 193–195°, $[\alpha]_D^{22}$ −138.9° (*c* 0.72, chloroform): R_F 0.42 (silica gel, 4:1 benzene–ethyl acetate); $\nu_{max}^{CHCl_3}$ 3400 (NH) and 1720 cm^{-1} (carbonyl): n.m.r. (100 MHz, $CDCl_3$): δ 1.27 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.73–2.01 (m, 2 H, SCH_2CH_2), 2.49–2.65 (m, 2 H, SCH_2), 2.79 –2.96 (m, 2 H, SCH_2), 3.17 (dd, 1 H, $J_{4',5'a}$ 4.6, $J_{5'a,5'b}$ 9.4 Hz, H-5'a), 3.45 (t, 1 H, $J_{4',5'b}$ 8.0 Hz, H-5'b), 3.99 (dd, 1 H, $J_{5,6}$ 1.6, $J_{2'',6}$ 4.0 Hz, H-6), 4.13–4.35 (m, 1 H, H-4'), 4.63 [d (partially obscured by H-2''), 1 H, $J_{3',4'}$ 6.0 Hz, H-3'], 4.69 (d, 1 H, SC*H*S), 4.81 (s, 1 H, H-2'), 5.07 (s, 1 H, H-1'), 5.12 (d, 1 H, H-5), 7.13–7.53 (m, 15 H, Ar), and 7.86 (broad s, 1 H, N*H*, exchangeable with D_2O). Irradiation of the doublet at δ 4.69 collapsed the doublet of doublets at δ 3.99 to a broad singlet. Irradiation of the multiplet at δ 4.13–4.35 collapsed the doublet at 4.63 to a singlet, and the triplet at δ 3.45 and the doublet of doublets at δ 3.17 collapsed to two doublets showing $J_{5'a,5'b}$ 9.4 Hz; *m/e* 726 (M^+ with ^{81}Br), 724 (M^+ with ^{79}Br), 711 ($M^+ - CH_3$), and 481 and 483 (M^+ − trityl).

Anal. Calc. for $C_{35}H_{37}BrN_2O_6S_2$: C, 57.93; H, 5.10; Br, 11.02; N, 3.86. Found: C, 57.59; H, 5.50; Br, 10.65; N, 3.58.

Continued elution of the column gave compound **6** as a white foam (0.66 g, 10%), which crystallized from carbon tetrachloride–hexane; m.p. 145–150° (amorphous), $[\alpha]_D^{22}$ +0.84° (*c* 1.7, chloroform): R_F 0.30 (4:1 benzene–ethyl acetate): $\nu_{max}^{CHCl_3}$ 3400 (NH) and 1720 cm^{-1} (carbonyl); n.m.r. (100 MHz, $CDCl_3$): δ 1.34 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 1.80–2.15 (m, 2 H, SCH_2CH_2), 2.76–3.03 (m,

4 H, SCH_2), 3.33 (d, 2 H, $J_{4',5'}$ 4.0 Hz, H-5'), 4.06 (dd, 1 H, $J_{2',6}$ 3.6, $J_{5,6}$ 6.0 Hz, H-6), 3.96–4.14 [m (buried under H-6), 1 H, H-4'], 4.50 (d, 1 H, SC*H*S), 4.73 (dd, 1 H, $J_{2',3'}$ 6.5, $J_{3',4'}$ 5.6 Hz, H-3'), 4.80 (d, 1 H, H-5), 5.30 (dd, 1 H, H-2'), 5.81 (d, 1 H, H-1'), 7.16–7.54 (m, 15 H, Ar), and 7.65 (broad s, 1 H, N*H*, exchangeable with D_2O). Irradiation of the doublet at δ 4.50 collapsed the doublet of doublets at δ 4.06 to a doublet ($J_{5,6}$ 6.0 Hz). Mass spectrum: *m/e* 711.1027. $C_{34}H_{34}{}^{81}BrN_2O_6S_2$ ($M^+ - CH_3$) requires 711.1022.

Anal. Calc. for $C_{35}H_{37}BrN_2O_6S_2$: C, 57.93; H, 5.10; N, 3.86. Found: C, 57.59; H, 4.94; N, 3.97.

Further elution of the column with 4:1 benzene–ethyl acetate gave compound **4** as a white glass (2.2 g, 37%) which crystallized from carbon tetrachloride–hexane: m.p. 138–139°, $[\alpha]_D^{22}$ −16.7° (*c* 0.6, chloroform); R_F 0.20 (4:1 benzene–ethyl acetate); $\nu_{max}^{CHCl_3}$ 3410 (NH) and 1710 cm^{-1} (carbonyl); n.m.r. (100 MHz, $CDCl_3$): δ 1.27 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.73–2.03 (m, 2 H, SCH_2CH_2), 2.48–2.71 (m, 2 H, H-5), 2.73–2.97 (m, 4 H, SCH_2), 3.18 (dd, 1 H, $J_{5'a,5'b}$ 9.4, $J_{4',5'a}$ 3.6 Hz, H-5'a), 3.46 (t, 1 H, $J_{4',5'b}$ 7.4 Hz, H-5'b), 3.67–3.95 (m, 1 H, H-4'), 4.11–4.27 (m, 1 H, H-6), 4.61 (d, 1 H, $J_{2',3'}$ 6.6 Hz, H-3'), 4.70 (d, 1 H, $J_{2',6}$ 3.2 Hz, SC*H*S), 5.09 (dd, 1 H, $J_{1',2'}$ 2.0 Hz, H-2'), 5.24 (d, 1 H, H-1'), 7.13–7.53 (m, 15 H, Ar), and 8.03 (broad s, 1 H, N*H*, exchangeable with D_2O): *m/e* 646 (M^+), 631 ($M^+ - CH_3$), 403 (M^+ — trityl).

Anal. Calc. for $C_{35}H_{38}S_2N_2O_6 \cdot 1.5\ H_2O$: C, 62.40; H, 6.09; N, 4.16. Found: C, 62.72; H, 5.80; N, 4.42.

Desulfurization of compound **4** *to give* (6S)-*5,6-dihydro-2',3'-O-isopropylidene-6-methyl-5'-O-trityluridine* (**7**). — A solution of the dithianyl compound **4** (132 mg) in ethanol (15 mL) and THF (2 mL) was boiled for 4 h under reflux in the presence of freshly activated Raney nickel. T.l.c. (3:1 benzene–ethyl acetate) showed a major, fluorescent component (R_F 0.32) contaminated with minor quantities of material having higher and lower R_F. The mixture was filtered, the nickel repeatedly washed with hot ethanol, and the combined filtrate and washings evaporated to a crude syrup (80 mg) that was chromatographed on silica gel (15 g) with 3:1 benzene–ethyl acetate as developer. The major component (**7**) was thus isolated as a white foam that was not crystallized (40 mg, 37%); $[\alpha]_D^{23}$ −32.0° (*c* 0.9, chloroform); n.m.r. (100 MHz, $CDCl_3$): δ 1.30 (s, 3 H, CMe_2), 1.36 (d, 3 H, J_{6,CH_3} 6.6 Hz, CH_3 of C-6), 1.52 (s, 3 H, CMe_2), 2.32 (d, 1 H, $J_{5a,5b}$ 16.6, $J_{5a,6}$ 0 Hz, H-5a), 2.80 (dd, 1 H, $J_{5b,6}$ 6.0 Hz, H-5b), 3.33 (dd, 2 H, $J_{4',5'a}$ 1.2, $J_{4',5'b}$ 3.2 Hz, H-5'a, H-5'b), 3.84–3.98 (broad t, 1 H, H-6), 4.12–4.28 (broad q, 1 H, H-4'), 4.70 (dd, 1 H, $J_{2',3'}$ 4.0, $J_{3',4'}$ 6.4 Hz, H-3'), 4.96 (dd, 1 H, H-2'), 5.46 (d, 1 H, H-1'), 7.16–7.52 (m, 15 H, Ar), and 7.68 (broad, s, 1 H, N*H*, exchangeable with D_2O): *m/e* 527 ($M^+ - CH_3$), 299 (M^+ — trityl).

Anal. Calc. for $C_{32}H_{34}N_2O_6$: C, 70.85; H, 6.27; N, 5.17. Found: C, 70.68; H, 6.40; N, 5.10.

(6R)-*5,6-Dihydro-6-(1,3-dithian-2-yl)uridine* (**8**). — A suspension of the protected nucleoside **4** (1.3 g) in 80% aqueous acetic acid was boiled for 30 min under

reflux, the resulting solution was cooled, and the solvents removed by repeated evaporation of xylene from the product. The residue was partitioned between water (100 mL) and chloroform (50 mL), the chloroform layer was drawn off, and the water layer was then washed with chloroform (2 × 40 mL). The water layer was evaporated and the resulting residue applied to a column (42 × 2.2 cm) of Bio-Rex 70 (H^+) cation-exchange resin. The column was then eluted with water, yielding compound **8** as a foam (425 mg, 60%) that crystallized from methanol–ethyl acetate: m.p. 190–191°, $[\alpha]_D^{23}$ −46.5° (*c* 0.9, methanol); R_F 0.29 (10:10:3 benzene–ethyl acetate–ethanol); λ_{max}^{MeOH} 245 nm (ε 1700); c.d. (*c* 5.23 × 10^{-4}, methanol) $\Delta\varepsilon_{250}$ −4.13; n.m.r. (100 MHz, Me_2SO-d_6): δ 1.90–2.20 (m, 2 H, SCH_2CH_2), 2.66–3.00 (m, 6 H, H-5, SCH_2), 3.50 (broad d, 2 H, $J_{4',5'}$ 3.2 Hz, H-5′), 3.71 (d, 1 H, H-4′), 3.90–4.20 (m, 3 H, H-2′, H-3′, H-6), 4.55 (d, 1 H, $J_{2',6}$ 3.6 Hz, SCHS), 4.84 (t, 1 H, $J_{5',OH}$ 5.6 Hz, CH_2OH, exchangeable with D_2O), 5.02 (d, 1 H, CHOH, exchangeable with D_2O), 5.25 (d, 1 H, CHOH, exchangeable with D_2O), 5.67 (d, 1 H, $J_{1',2'}$ 6.8 Hz, H-1′), and 10.42 (s, 1 H, NH, exchangeable with D_2O).

Anal. Calc. for $C_{13}H_{20}N_2O_6S_2$: C, 42.86; H, 5.49; N, 7.69. Found: C, 42.62; H, 5.54; N, 7.61.

(*6*R)-*5,6-Dihydro-6-(1,3-dithian-2-yl)uracil* (**9**). — A solution of nucleoside **8** (35 mg) in M hydrochloric acid (4 mL) was heated for 4 h at 80°. The mixture was then cooled to afford colourless needles that were isolated by filtration and recrystallized from methanol, yielding pure **9** (10 mg, 45%), m.p. 258.5–250° (lit.[16] m.p. 260–261°): $[\alpha]_D^{22}$ −60.4° (*c* 0.2, methanol); n.m.r. (100 MHz, Me_2SO-d_6): δ 1.48–2.18 (m, 2 H, SCH_2CH_2), 2.58–2.98 (m, 6 H, H-5, SCH_2), 3.63–3.92 (m, 1 H, H-6), 4.24 (d, 1 H, $J_{1',6}$ 6.0 Hz, H-1′), 7.58 (broad s, 1 H, NH, exchangeable with D_2O), and 10.08 (broad s, 1 H, NH, exchangeable with D_2O).

(*6*R,S)-*5,6-Dihydro-6-formyl-2′,3′*-O-*isopropylidene-5′*-O-*trityluridine* (**10**) (*as semicarbazone* **11**). — A mixture of nucleoside **4** (380 mg), barium carbonate (325 mg), and methyl iodide (2 mL) in 15% aqueous acetone (17 mL) was heated for 48 h at 55°. The cooled mixture was then filtered to remove the barium salts, the filtrate evaporated, and the residue dissolved in chloroform (200 mL). The solution was washed with water (3 × 40 mL), dried, and evaporated to a pale-yellow syrup that was dissolved in methanol (10 mL) and pyridine (0.5 mL), and 0.5M aqueous semicarbazide hydrochloride (1 mL) was added. The solution was then heated for 10 min on a steam bath, the solvents evaporated, and the residue suspended in ethyl acetate (75 mL) and washed with water (3 × 20 mL). The organic layer was dried and evaporated to a crude syrup that was purified chromatographically on silica gel (30 g) with 9:1 benzene–ethanol as developer, yielding the semicarbazone **11** (100 mg; 30% from **4**) as a solid which was recrystallized twice from toluene–hexane: m.p. 160–162°, $[\alpha]_D^{23}$ +23.5° (*c* 0.84, methanol); R_F 0.22 (9:1 benzene–ethanol); $\nu_{max}^{CHCl_3}$ 3495 (NH_2), 3340 (N–NH), 3210 (CONHCO), 1725 (pyrimidine C=O), 1700 ($-CONH_2$), 1640 (C=N), and 1590 cm^{-1} (Amide II); n.m.r. (100 MHz, $CDCl_3$): δ 1.30 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 2.56 (dd, 1 H, $J_{5a,6}$ 6.0, $J_{5a,b}$ 17.0 Hz, H-5a), 2.86 (d, 1 H, $J_{5b,6}$ 0 Hz, H-5b), 3.33 (broad s, 2 H, H-5′), 4.15 (d, 1 H, $J_{3',4'}$ 3.0 Hz,

H-4'), 4.47–4.86 (m, 3 H, H-2', H-3', H-6), 5.99 (d, 1 H, $J_{1',2'}$ 4.0 Hz, H-1'), 6.06 (broad s, 2 H, NH_2, exchangeable with D_2O), 6.98 (d, 1 H, $J_{1'',6}$ 10.0 Hz, C*H*=N), 7.12–7.50 (m, 15 H, aromatic), 9.12 (broad s, 1 H, NH, exchangeable with D_2O), and 10.31 (broad s, 1 H, NH, exchangeable with D_2O).

Anal. Calc. for $C_{33}H_{35}N_5O_7 \cdot 0.5\ H_2O$: C, 63.67; H, 5.79; N, 11.25. Found: C, 63.64; H, 5.68; N, 11.16.

Debromination of compound **5** *to give compound* **4**. — A solution of **5** (140 mg) in ethanol (10 mL) and THF (2 mL) containing freshly activated Raney nickel was heated for 1 h at 90°. T.l.c. (4:1 benzene–ethyl acetate) showed that a single new compound of R_F 0.20 had been formed. The mixture was filtered, the nickel washed repeatedly with ethanol, the combined filtrate and washings evaporated, and the residual syrup chromatographed on silica gel (17 g). Elution with 4:1 benzene–ethyl acetate gave compound **4** as a foam (54 mg, 44%), $[\alpha]_D^{23}$ −13.0° (*c* 1.0, chloroform). The i.r., n.m.r., and mass spectra of **4** obtained from **5** were identical to those of **4** obtained directly from **2**.

Debromination of compound **6** *to give compound* **4**. — Treatment of **6** (100 mg) with Raney nickel as for **5** gave **4** (30 mg, 33%), $[\alpha]_D^{23}$ −14.2° (*c* 1, chloroform), identical by R_F value and n.m.r. data with that obtained from compounds **5** and **2**.

6-Formyl-2',3'-O-isopropylidene-5'-O-trityluridine (**12**) *and 6-formyl-2',3'-O-isopropylidene-3-methyl-5'-O-trityluridine* (**13**) (*characterized as the semicarbazones* **14** *and* **15**, *respectively*) *from compound* **5**. — A mixture of **5** (300 mg), barium carbonate (660 mg), methyl iodide (1 mL, added at 12-h intervals), and dimethyl sulfoxide (1.5 mL) in 10% aqueous acetone (17 mL) was heated for 72 h at 55° under nitrogen. T.l.c. (4:1 benzene–ethyl acetate) showed complete consumption of starting material with the formation of two components of R_F 0.13 and 0.23 (compounds **12** and **13**, respectively). The mixture was processed as before (see compound **10**), leaving a yellow syrup; n.m.r. (100 MHz, $CDCl_3$): δ 9.53 (s, C*H*=O). Without further purification, the aldehyde was treated with semicarbazide hydrochloride as before (see compound **11**). Two semicarbazones were formed, which were separated by preparative t.l.c. on silica gel with 15:1 benzene–ethanol. The slower-moving component was shown to be compound **14** (22 mg from 48 mg of crude 6-aldehyde; 41%), which was crystallized from ethanol–benzene–hexane, m.p. 211–212°, $[\alpha]_D^{22}$ −17.5° (*c* 0.51, acetone): R_F 0.21 (9:1 benzene–ethanol); $\nu_{max}^{CHCl_3}$ 3540 (NH_2), 3400 (NH_2), 3200 (NH), 1700 (broad C=O stretch), and 1580–1620 cm^{-1} (complex pattern, C=C, C=N, Amide II); n.m.r. (100 MHz, Me_2SO-d_6): δ 1.04 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 2.73–3.42 (m, 2 H, H-5'), 3.78–4.02 (m, 1 H, H-4'), 4.48 (broad t, 1 H, $J_{3',4'}$ 5.0 Hz, H-3'), 5.00 (d, 1 H, $J_{2',3'}$ 6.0 Hz, H-2'), 5.96 (s, 2 H, H-5, H-1'), 6.56 (broad s, 2 H, NH_2, exchangeable with D_2O), 7.06–7.30 (m, 15 H, Ar), 7.56 (s, 1 H, –CH=N), 10.54 (s, 1 H, NH, exchangeable with D_2O), and 11.20 (s, 1 H, NH, exchangeable with D_2O).

Anal. Calc. for $C_{33}H_{33}N_5O_7 \cdot 0.5\ H_2O$: C, 63.87; H, 5.48; N, 11.29. Found: C, 63.85; H, 5.42; N, 11.19.

The faster-migrating component (compound **15**) was obtained as a solid (7 mg,

13%), m.p. 213–215°, which could not be crystallized owing to the formation of a gel in organic solvents; $[\alpha]_D^{23}$ −5.6° (*c* 0.23, methanol); R_F 0.30 (9:1 benzene–ethanol); $\nu_{max}^{CHCl_3}$ 3540 (NH_2), 3375 (NH), 3200 (NH), 1700 (pyrimidine C=O), 1675 (amide C=O), and 1620–1565 cm^{-1} (complex pattern due to C=C, C=N, amide II); n.m.r. (100 MHz, Me_2SO-d_6): δ 1.28 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 2.98 (s, 3 H, NCH_3), 3.00–3.54 [m (obscured by water peak), 2 H, H-5′], 4.00–4.34 (m, 1 H, H-4′), 4.77 (broad t, $J_{3',4'}$ 5.0 Hz, H-3′), 5.24 (d, 1 H, $J_{2',3'}$ 6.0 Hz, H-2′), 6.26 (s, 1 H, H-1′), 6.34 (s, 1 H, H-5), 6.80 (broad s, 2 H, NH_2, exchangeable with D_2O), 7.20–7.60 (m, 15 H, Ar), 7.80 (s, 1 H, C*H*=N), and 10.82 (s, 1 H, NH, exchangeable with D_2O); *m/e* 567 (M^+ − acetone), 539 (M^+ − CH=NNHCONH$_2$), 415 (M^+ − base), and 382 (M^+ − trityl).

Anal. Calc. for $C_{34}H_{35}N_5O_7 \cdot H_2O$: C, 63.45; H, 5.75; N, 10.88. Found: C, 63.87; H, 5.47; N, 10.58.

Compounds **12** *and* **13** (*characterized as semicarbazones* **14** *and* **15**, *respectively*) *from compound* **6**. — Treatment of **6** (136 mg) with methyl iodide as for compound **5** gave, after formation and purification of the semicarbazones, compound **14** (34 mg, 30%), m.p. 209–211°, $[\alpha]_D^{23}$ −19.4° (*c* 0.9, acetone). The R_f, i.r., and n.m.r. data were identical with those obtained for **14** derived from **5**.

Semicarbazone **15** was also isolated (6 mg, 5%): m.p. 209–214°, $[\alpha]_D^{23}$ −4.0° (*c* 0.25, methanol). The R_f and n.m.r. data for **15** were identical with those described previously.

6-(Hydroxymethyl)-2′,3′-O-isopropylidene-5′-O-trityluridine (**16**). — To a solution of the 6-aldehyde **12** (232 mg) in ethanol (8 mL) was added dropwise a solution of sodium borohydride (20 mg) in ethanol (4 mL). The mixture was stirred for 1 h at room temperature, concentrated to one-third its volume, diluted with ether (150 mL), and successively washed with M hydrochloric acid (2 × 20 mL), saturated aqueous sodium hydrogencarbonate (2 × 20 mL), and water (3 × 15 mL). The ether layer was dried and evaporated to afford a clear syrup (202 mg). Boric acid complexes were removed from this crude product by repeatedly evaporating methanol from it. The syrup thus obtained was chromatographed on silica gel (60 g) with 1:1 benzene–ethyl acetate as developer. The component having R_F 0.21 (**16**) was isolated as a colourless oil that could not be crystallized (168 mg, 72%). $[\alpha]_D^{23}$ +14.1° (*c* 0.73, chloroform); $\nu_{max}^{CHCl_3}$ 3600–3300 (broad, OH), 3420 (NH), 1700 (C=O), and 1610 cm^{-1} (weak C=C): n.m.r. (100 MHz, $CDCl_3$): δ 1.26 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.54 (s, 1 H, OH, exchangeable with D_2O), 3.16 (dd, 1 H, $J_{4',5'a}$ 4.0, $J_{5'a,5'b}$ 9.6 Hz, H-5′a), 3.44 (dd, 1 H, $J_{4',5'b}$ 8.0 Hz, H-5′b), 4.22–4.38 (m, 1 H, H-4′), 4.58 (s, 2 H, CH_2OH, changes to doublet with J_{gem} 6.4 Hz upon addition of D_2O), 4.72 (dd, 1 H, $J_{2',3'}$ 7.0, $J_{3',4'}$ 4.0 Hz, H-3′) 5.15 (d, 1 H, H-2′), 5.74 (s, 1 H, H-1′), 5.86 (s, 1 H, H-5), 7.12–7.50 (m, 15 H, Ar), and 8.06 (broad s, ~1 H, NH, exchangeable with D_2O); *m/e* 541 (M^+ − CH_3), 313 (M^+ − trityl), 126 (H^+ base).

Anal. Calc. for $C_{32}H_{32}N_2O_7 \cdot 0.5\ H_2O$: C, 67.96; H, 5.84; N, 4.96. Found: C, 68.10; H, 5.73; N, 4.93.

6-(Hydroxymethyl)uridine (**17**). — A solution of the protected nucleoside **16**

(68 mg) in 80% aqueous acetic acid (3 mL) was boiled for 25 min under reflux, cooled, and evaporated. Traces of acid were removed by evaporation of xylene from the residue. The resulting, crude solid was suspended in water (30 mL) and washed with chloroform (3 × 15 mL). The water layer was then concentrated, applied to a column of Bio-Rex 70 (H^+) cation-exchange resin (30 × 1.65 cm), and the column eluted with water to yield the free nucleoside **17** as a clear syrup (23 mg, 69%), $[\alpha]_D^{23}$ −31.8° (*c* 1.5, methanol); λ_{max}^{MeOH} 258 nm (ε 6080); n.m.r. (100 MHz, Me_2SO-d_6): δ 3.40–3.64 (m, 2 H, H-5′), 3.67–3.82 (m, 1 H, H-4′), 4.02–4.21 (m, 1 H, collapses to a triplet upon addition of D_2O, $J_{3',4'}$ 6.0 Hz, H-3′), 4.39 (s, 2 H, C*H*$_2$ of C-6), 4.50–4.71 (m, 2 H, partly exchanges with D_2O, leaving dd, $J_{2',3'}$ 6.0, $J_{1',2'}$ 4.0 Hz, H-2′, O*H*-5′), 4.92 (d, 1 H, O*H*, exchangeable with D_2O), 5.16 (d, 1 H, O*H*, exchangeable with D_2O), 5.41 (d, 1 H, H-1′), 5.75 (broad s, 2 H, partly exchanges with D_2O, leaving a sharp singlet, H-5, CH_2OH of C-6), and 11.29 (broad s, 1 H, NH, exchangeable with D_2O).

Anal. Calc. for $C_{10}H_{14}N_2O_7 \cdot 0.5\ H_2O$: C, 42.40; H, 5.30; N, 9.89. Found: C, 42.66; H, 5.21; N, 9.75.

6-(Hydroxymethyl)uracil (**18**). — A solution of nucleoside **17** (15 mg) in M hydrochloric acid (2 mL) was heated for 12 h at 90°, cooled, and made neutral with an excess of solid barium carbonate. The undissolved salt was removed by filtration, the filtrate evaporated, and the crude residue chromatographed on a column of Bio-Rex 70 (H^+) resin that was developed with water. The first component to be eluted was ribose, which was identified by chromatography on Whatman No. 1 paper (descending elution with water-saturated butanol) against authentic D-ribose (R_F 0.17, paper gram, alkaline silver nitrate detection). Continued elution of the resin column gave compound **18** as a white powder (6 mg, 76%), which was crystallized from water; m.p. 269–270° (dec.) (lit.[45] m.p. 274° (dec.); n.m.r. (100 MHz, Me_2SO-d_6): δ 4.19 (s, 2 H, C*H*$_2$), 5.50 (s, 1 H, H-5), and 10.60–11.04 (broad band, ~2 H, NH, exchanges with D_2O [lit.[44] n.m.r., 60 MHz, D_2O: δ 4.17 (CH_2)].

E- (*or* Z)-6-[*2-Cyano-2-(ethoxycarbonyl)ethylidene*]-*2′,3′*-O-*isopropylidene-5′*-O-*trityluridine* (**19**) *and* E- (*or* Z-)*6*-[*2-cyano-2-(ethoxycarbonyl)ethylidene*]-*2′,3′*-O-*isopropylidene-3-methyl-5′*-O-*trityluridine* (**20**). — A solution of the crude aldehyde mixture (**12** and **13**, 1.42 g), ethyl cyanoacetate (3.5 mL), and ammonium acetate (20 mg) in anhydrous *N,N*-dimethylformamide (50 mL) was stirred under nitrogen for 2 h at room temperature. The mixture was then diluted with ether (300 mL) and washed with water (3 × 40 mL). The dried ether layer was evaporated to a yellow syrup that was chromatographed on silica gel (200 g) with 5:1 benzene–ethyl acetate as developer. The faster moving, minor component was shown to be **20** (168 mg, 10%) and was crystallized from ether–hexane; m.p. 104–105°, $[\alpha]_D^{23}$ +2.79° (*c* 0.61, chloroform); R_F 0.35 (4:1 benzene–ethyl acetate); $\nu_{max}^{CCl_4}$ 1745 (ester C=O), 1725 (pyrimidine C=O), 1680 (pyrimidine C=O), and 1630 cm^{-1} (C=C); n.m.r. (100 MHz, $CDCl_3$): δ 1.31 (s, 3 H, CH_3), 1.44 (t, 3 H, $J_{CH_2CH_3}$ 7.2 Hz, CH_2CH_3), 1.54 (s, 3 H, CH_3), 3.14 (s, 3 H, N*CH*$_3$), 3.26 (dd, 1 H, $J_{4',5'a}$ 4.0, $J_{5'a,5'b}$ 10.5 Hz, H-5′a), 3.46 (t, 1 H, $J_{4',5'b}$ 8.0 Hz, H-5′b), 4.25–4.50 (m, 1 H, H-4′), 4.46 [q (partially ob-

scured by H-4'), 2 H, CH_2CH_3], 4.81 (dd, 1 H, $J_{2',3'}$ 6.0, $J_{3',4'}$ 4.0 Hz, H-3'), 5.18 (d, 1 H, H-2'), 5.44 (s, 1 H, H-1'), 6.20 (s, 1 H, H-5), 7.18–7.60 (m, 15 H, aromatic), and 8.12 (s, 1 H, C*H*=C–CN); *m/e* 663 (M^+), 648 ($M^+ - CH_3$), 420 (M^+ — trityl), 415 (M^+ — base).

Anal. Calc. for $C_{38}H_{37}N_3O_8 \cdot 0.5\ H_2O$: C, 67.85; H, 5.65; N, 6.25. Found: C, 68.21; H, 5.49; N, 6.16.

The major and slower-moving component, compound **19**, was isolated as a foam (0.63 g, 38%) and crystallized from ether–hexane; m.p. 122–123°, $[\alpha]_D^{23}$ +0.18° (*c* 1.1, chloroform); R_F 0.16 (4:1 benzene–ethyl acetate); $\nu_{max}^{CCl_4}$ 3420 (NH), 3200 (NH), 1725 (ester C=O), 1715 (pyrimidine C=O), 1705 (pyrimidine C=O), and 1635 cm^{-1} (C=C); n.m.r. (100 MHz, $CDCl_3$): δ 1.26 (s, 3 H, CH_3), 1.38 (t, 3 H, $J_{CH_2CH_3}$ 7.0 Hz, CH_2–C*H*$_3$), 1.52 (d, 3 H, CH_3), 3.22 (dd, 1 H, $J_{4',5'a}$ 5.0, $J_{4,5'b}$ 10.0 Hz, H-5'a), 3.40 (t, 1 H, $J_{5'a,5'b}$ 8.0 Hz, H-5'b), 4.20–4.39 (m, 1 H, H-4'), 4.41 [q (partially obscured by H-4'), 2 H, C*H*$_2$–CH_3], 4.71 (dd, 1 H, $J_{2',3'}$ 6.8, $J_{3',4'}$ 3.6 Hz, H-3'), 5.12 (d, 1 H, H-3'), 5.36 (s, 1 H, H-1'), 6.08 (s, 1 H, H-5), 7.14–7.54 (m, 15 H, aromatic), 8.05 (s, 1 H, C*H*=C–CN), and 8.82 (s, 1 H, NH, exchangeable with D_2O); *m/e* 649 (M^+), 635 ($M^+ - CH_3$), 415 (M^+ — base), 406 (M^+ — trityl).

Anal. Calc. for $C_{37}H_{35}N_3O_8$: C, 68.41; H, 5.39; N, 6.47. Found: C, 67.95; H, 5.36; N, 6.19.

R-(*or* S-)*6-[(2-Acetamidomethyl-2-ethoxycarbonyl)ethyl]-2',3'-O-isopropylidene-5'-O-trityluridine* (**21**). — A solution of the cyano derivative **19** (150 mg) in anhydrous acetic anhydride (20 mL) was hydrogenated at 50 $lb.in^{-2}$ for 20 h at room temperature in the presence of platinum oxide (20 mg) as catalyst. The mixture was then diluted with chloroform (150 mL) and filtered through a Celite pad to remove the catalyst. The filtrate was evaporated and traces of acetic anhydride removed by repeated evaporation of toluene from the residue, which was then applied to a column of silica gel (30 g). The column was developed with 9:1 benzene–ethanol, and the component having R_F 0.29 isolated as a white foam (80 mg, 50%): $[\alpha]_D^{23}$ +2.97° (*c* 0.8, chloroform); n.m.r. (100 MHz, $CDCl_3$): δ 0.92–1.28 (m, ~6 H, CH_2CH_3, CH_3 of CMe_2), 1.40 (d, ~3 H, CH_3 of CMe_2), 1.80, 1.90, 1.95 (3s, 3 H, N*Ac*), 2.32–3.62 (m, ~7 H, H-5', CH_2CHCH_2), 3.82–4.37 (m, 3 H, H-4', CH_2CH_3), 4.62–4.74 (m, 1 H, H-3'), 4.94–5.28 (m, 1 H, H-2'), 5.64 (s, 1 H, H-5), 5.70 (d, 1 H, H-1'), 5.85 (broad s, 1 H, N*H*, exchangeable with D_2O), 7.08–7.48 (m, ~15 H, aromatic), and 8.10 (broad s, 1 H, N*H*, exchangeable with D_2O); *m/e* 697 (M^+), 682 ($M^+ - CH_3$), 454 (M^+ — trityl). A signal was also observed at *m/e* 709, indicating partial saturation of the trityl group.

Anal. Calc. for $C_{39}H_{43}N_3O_9$: C, 67.14; H, 6.17; N, 6.03. Found: C, 66.88; H, 6.47; N, 5.80.

R-(*or* S-)*6-[2-Acetamidomethyl-2-(ethoxycarbonyl)ethyl]uridine* (**22**). — A solution of the protected nucleoside **21** (80 mg) in 80% aqueous trifluoroacetic acid (4 mL) was stirred for 15 min at room temperature. The yellow solution was then diluted with methanol (30 mL) and toluene (100 mL), and evaporated to near dryness.

Azeotropic evaporation of toluene was repeated (5 × 30 mL) in order to remove traces of acid, finally yielding a clear syrup that was purified by chromatography on a column of Bio-Rex 70 (H^+) resin (29 × 1.7 cm). Elution with water afforded the pure nucleoside derivative **22** as a syrup (34 mg, 72%), $[\alpha]_D^{23}$ −19.1° (*c* 1.4, methanol); R_F 0.16 (5:1 ethyl acetate–ethanol); λ_{max}^{MeOH} 260 nm (ε 12,540); c.d. (*c* 4.1 × 10^{-}e, water) $\Delta\varepsilon_{260}$ −0.29; n.m.r. (100 MHz, Me_2SO-d_6): δ 1.21 (t, 3 H, *J* 7.0 Hz, CH_2CH_3), 1.87 (s, 3 H, NH*Ac*), 2.87 (broad s, 3 H, CH_2CHCO_2), 3.23–3.89 (m, 5 H, H-5′, H-4′, CH_2NH), 4.14 (q, 3 H, CH_2CH_3, H-3′), 4.55 (dd, 1 H, $J_{2',3'}$ 6.0, $J_{1',2'}$ 4.0 Hz, H-2′), 4.73 [t (partially obscured by H-2′), 1 H, CH_2OH, exchangeable with D_2O], 5.01 (broad s, 1 H, O*H*, exchangeable with D_2O), 5.23 (broad s, 1 H, O*H*, exchangeable with D_2O), 5.43 (pseudo-t, 1 H, H-1′), 5.55 (s, 1 H, H-5), 8.08 (d, 1 H, N*H*Ac, exchangeable with D_2O), and 11.39 (broad s, 1 H, N*H* of pyrimidine, exchangeable with D_2O).

Anal. Calc. for $C_{17}H_{25}N_3O_9 \cdot H_2O$: C, 47.11; H, 6.23; N, 9.69. Found: C, 47.03; H, 6.00; N, 9.11.

R- (*or* S-)*6-[(2-Aminomethyl-2-ethoxycarbonyl)ethyl]-2′,3′-O-isopropylidene-5′-O-trityluridine* (**23**). — A solution of the cyano compound **19** (250 mg) in methanol was hydrogenated for 2 h at 50 lb.in.$^{-2}$ in the presence of platinum oxide (40 mg). The mixture was filtered to remove the catalyst and the filtrate evaporated to a crude solid (260 mg) that was chromatographed on a column of silica gel (40 g). Elution of the column with 2:1 benzene–ethyl acetate yielded the amine **23** (109 mg, 43%), $[\alpha]_D^{23}$ +4.7° (*c* 1.1, chloroform); R_F 0.48 (15:1 benzene–ethanol); $\nu_{max}^{CCl_4}$ 3400 (NH_2), 3180 (NH_2), 1755 (ester C=O), 1700 (pyrimidine C=O), and 1620 cm^{-1} (C=C); n.m.r. (100 MHz, $CDCl_3$): δ 1.24 (t, 3 H, CH_2CH_3), 1.30 (s, 3 H, CMe_2), 1.54 (s, 3 H, CMe_2), 1.74 (broad s, 2 H, NH_2, exchangeable with D_2O), 2.90–3.60 (m, 4 H, H-5′, C=C-CH_2), 3.82 (d, 2 H, CH_2NH_2), 4.00–4.46 (m, 4 H, H-4′, $CHCO_2CH_2$), 4.72 (m, 1 H, H-3′), 5.18 (d, 1 H, $J_{2',3'}$, 6.0 Hz, H-2′), 5.60 (s, 1 H, H-1′), 5.74 (s, 1 H, H-5), 7.04–7.60 (m, 15 H, aromatic), and 8.70 (broad s, 1 H, NH, exchangeable with D_2O).

Anal. Calc. for $C_{37}H_{41}N_3O_8 \cdot 0.1\ CCl_4$: C, 66.39; H, 6.11; N, 6.26. Found: C, 66.76; H, 5.75; N, 5.96.

Carbon tetrachloride was used in preparing the analytical sample of **23**, which explains its presence in the subsequent analysis.

R-(*or* S-)*6-(3-Amino-2-carboxypropyl)uridine* (**24**). — A solution of nucleoside **23** (52 mg) in 90% aqueous trifluoroacetic acid (5 mL) was stirred for 10 min at room temperature. The mixture was then diluted with toluene (50 mL) and the solution evaporated at <35°. Traces of acid were removed from the residue by repeated evaporation of toluene from the product. The residue was then suspended in water (30 mL) and the mixture washed with dichloromethane (3 × 10 mL). The aqueous layer was evaporated to a hard syrup which, without further purification, was dissolved in methanol (5 mL). To this solution was added 3M methanolic sodium methoxide (60 μL) and water (0.2 mL). After 12 h at room temperature, Bio-Rex 70 (H^+) cation-exchange resin was added to remove sodium ions, and the

mixture was filtered and the filtrate evaporated. The residue was then chromatographed on a column of Bio-Rex 70 (H^+) resin with water as the developer. The fractions containing fluorescent material were combined, yielding the free nucleoside **24** as a syrup (17 mg: 62%), $[\alpha]_D^{23}$ +1.3° (*c* 0.8, water): $\lambda_{max}^{H_2O}$ 260 nm (ε 11,500); n.m.r. (100 MHz, Me_2SO-d_6): 2.80–3.20 (m, 3 H, CH_2CH), 3.30–3.90 (m, 5 H, H-4′, H-5′, CH_2NH_2), 3.98–4.20 (m, 1 H, H-3′), 4.20–5.20 (broad band, 6 H, collapses to pseudo-t of H-2′ upon addition of D_2O), 5.46 (s, 1 H, H-1′), 5.68 (s, 1 H, H-5), and 7.45 (broad band, 2 H, NH_2, exchangeable with D_2O); *m/e* 243 (M^+ — CH_2–Alanine), 166 (base — CO_2H).

Compound **24** (5 mg) was dissolved in anhydrous methanol (1.5 mL) and a 3.2M solution of hydrogen chloride in ether (20 μL) was added at 0°. After 1 h at 0°, ether (3 mL) was added to the solution, and the hydrochloride salt of **24** precipitated and was collected by filtration.

Anal. Calc. for $C_{13}H_{19}N_3O_8 \cdot 1.5$ HCl: C, 39.00; H, 5.13; N, 10.50. Found: C, 39.35; H, 4.67; N, 12.37.

Insufficient material was available to determine the exact proportion of HCl: the stereochemistry of the side chain at C-6 could not be ascertained.

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