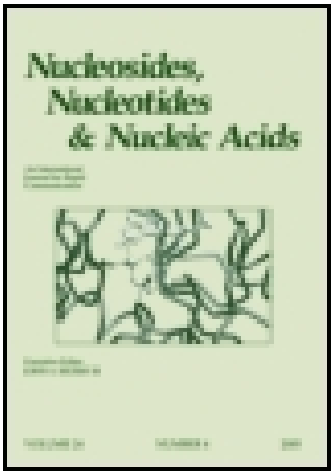

Nucleosides and Nucleotides
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn19

The Synthesis of 4′-t-Butylcarbamyl- and 4′-p-Toluenesulphonamidyl-2′,3′-Dideoxy Pyrimidine Nucleoside Analogues

Lea Pickering [a], Baljinder S. Malhi [a b], Paul L. Coe [a] & Richard T. Walker [a]

[a] School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, U.K., B15 2TT

[b] The Wellcome Foundation Ltd., South Eden Park Rd, Beckenham, Kent, UK

Published online: 24 Sep 2006.

To cite this article: Lea Pickering, Baljinder S. Malhi, Paul L. Coe & Richard T. Walker (1994) The Synthesis of 4′-t-Butylcarbamyl- and 4′-p-Toluenesulphonamidyl-2′,3′-Dideoxy Pyrimidine Nucleoside Analogues, Nucleosides and Nucleotides, 13:6-7, 1493-1506, DOI: 10.1080/15257779408012166

To link to this article: http://dx.doi.org/10.1080/15257779408012166

NUCLEOSIDES & NUCLEOTIDES, 13(6&7), 1493-1506 (1994)

THE SYNTHESIS OF 4'-*t*-BUTYLCARBAMYL- AND 4'-*p*-TOLUENESULPHONAMIDYL-2',3'-DIDEOXY PYRIMIDINE NUCLEOSIDE ANALOGUES

Lea Pickering, Baljinder S.Malhi,† Paul L.Coe, Richard T.Walker*
School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, U.K., B15 2TT.

ABSTRACT: The preparation of 4'-*t*-butylcarbamyl-2',3'-dideoxy thymidine, uridine and 5-ethyl uridine nucleoside analogues and 4'-*p*-toluenesulphonamidyl-2',3'-dideoxy thymidine and 5-ethyl uridine nucleoside analogues from L-pyroglutamic acid is reported.

The continued efforts to develop nucleosides as effective anticancer and antiviral agents have led to a great variety of analogues of this class of compound. In recent times, nucleosides with modified sugars have been shown to be promising antiviral and anticancer compounds, notably those in which the ribose sugar ring is replaced by a different 5-membered heterocycle containing sulphur, sulphur and oxygen or isomeric arrangements of one or two oxygen heteroatoms. Compounds such as dioxolane-T,[1] 4'-thiothymidine[2] and the oxathiolane nucleosides such as BCH-189[3] have displayed potent antiviral properties. The replacement of the furanose ring with an amino-sugar or pyrrolidine moiety has also been investigated.

Examples of this class of nucleoside analogue include (Figure 1) 1'-amino-nucleosides **(A)**,[4] which contain an N-N glycosidic linkage, 3'-amino-nucleosides **(B)**[5] and 4'-acetamido- analogues **(C)**. The latter include amino-sugar analogues of ribose and lyxose.[6] With the exception of the tiazofurin analogue **(D)**, which contains a C-C glycosidic link, none of the 4'-amino- analogues has an unprotected nitrogen heteroatom.

Dedicated to Dr.Morio Ikehara on the occasion of his 70th birthday.

†Current address: The Wellcome Foundation Ltd., South Eden Park Rd, Beckenham, Kent, UK.

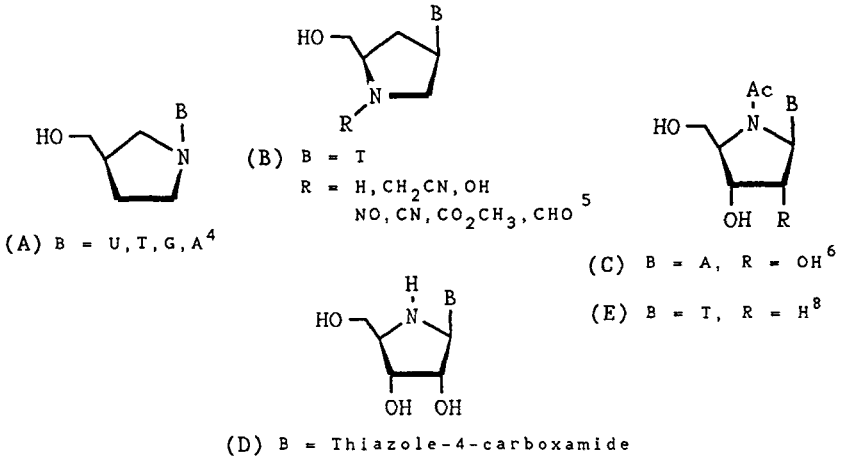

FIGURE 1

None of the aforementioned 4'-amino-sugar nucleosides has been tested for antiviral activity. For this reason we decided to synthesise and evaluate a series of 4'-amino-sugar nucleosides which could be potential antiviral agents. Dideoxy nucleosides such as ddI, ddC and ddA[7] have shown strong antiviral activity, and so a 4'-amino-sugar analogue of such compounds seemed an ideal target compound.

Very recently the synthesis of a 4'-acetamido thymidine analogue (**E**) was reported,[8] also with the aim of producing a biologically active compound, confirming the renewed interest in this class of nucleoside analogue.

CHEMISTRY

The chosen starting material, L-pyroglutamic acid (**1**)(Figure 2), proved to have the correct configuration to give dideoxy 4'-amino-sugar nucleosides which mimic the D-configuration found in natural nucleosides and in many of the biologically active unnatural analogues. Conversion to the methyl ester (**2**) was achieved with $SOCl_2$ and methanol.[9] Reduction of the ester with sodium borohydride[9] yielded the alcohol (**3**), which was subsequently protected as the silyl ether (**4**). Treatment with di-*t*-butyl dicarbonate under basic conditions, afforded the protected lactam (**5**) according to published methods.[10]

Elaboration of the lactam to a dideoxy nucleoside analogue was *via* reduction to the a-hydroxy-*N*-*t*-BOC pyrrolidine (**6**). Treatment of **6** with stannic chloride or trimethylsilyl trifluoromethanesulphonate (TMSOTf) in the presence of 2,4-*bis*-*O*-(trimethylsilyl)thymine yielded the protected nucleoside analogue (**7**) in 18% yield. The α-hydroxy compound **6**

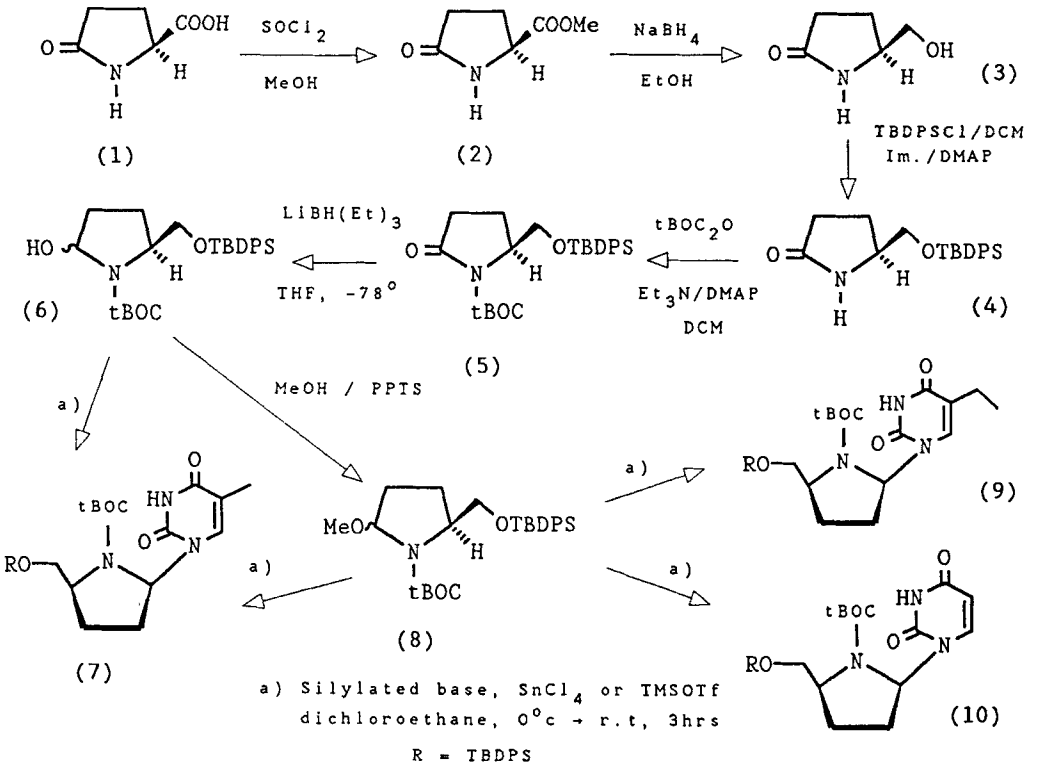

FIGURE 2

was found to be slightly unstable and it was converted to the more stable α-methoxy-*N*-*t*-BOC pyrrolidine (**8**). From the latter compound, thymine, uracil (**9**), and 5-ethyluracil (**10**) derivatives were prepared by the same method as for **7**. Yields of these compounds were also low at 26%, 13% and 18% respectivley. Proton n.m.r of the nucleosides (**7**),(**9**) and (**10**) showed that four isomeric compounds were present in each case: two arising from the α- and β-anomers formed during the condensation reaction, and a further two isomers caused by the restricted rotation of the *t*-BOC group about the C-N bond. Variable temperature 400MHz n.m.r measurements showed coalesence of two pairs of signals from the *t*-BOC group at 57°C, to give just one pair of signals arising from the mixture of α- and β-anomers.

The restriction of rotation of the *t*-BOC group, supplied a possible explanation for the low yields observed in these reactions. On treatment with a Lewis acid, an iminium ion is generated from the α-hydroxy or α-methoxy pyrrolidines. Stabilisation of these ions is

dependent on the nature of the substituent groups on the nitrogen atom.[11] With acyl groups, such as *t*-BOC, this is only possible when the *t*-BOC carbonyl function is planar with the iminium ion.[11] In the case of the *N*-*t*-BOC pyrrolidines, the restricted rotation of the *t*-BOC group causes the iminium ion to be insufficiently stabilised and so is lost in a side reaction involving elimination of a proton to give a cyclic enamine before it can react with the silylated base.

This finding had also been reported by groups working in other areas using iminium ions in their synthetic strategies. Somfai and Ahman had found that better yields were obtained when the tosyl group was used to protect the nitrogen.[12] To investigate this an *N*-tosyl pyrrolidine was prepared according to their protocol.[13] From the silyl ether **(4)**(Figure 3), protection of the nitrogen was achieved by treatment with lithium hexamethyldisilazide followed by quenching of the amidate anion with tosyl chloride to give the toluenesulphonamide **(11)**. Reduction of **11** with DIBAL-H yielded the a-hydroxy-*N*-tosyl pyrrolidine **(12)**, which was subsequently converted to the α-methoxy-*N*-tosyl pyrrolidine **(13)**. Treatment of pyrrolidine **(13)** with stannic chloride in the presence of *bis*-trimethylsilyloxy-thymine gave the nucleoside **(14)** in good yield. Similar treatment of **13** with 2,4-*bis*-*O*-(trimethylsilyl)-5-ethyl uracil afforded nucleoside analogue **(15)** in 53% yield. Both nucleoside analogues were obtained as inseparable anomeric mixtures.

Deprotection of the 5'-hydroxyl function for the purposes of biological testing was easily accomplished for all analogues by treatment with tetrabutylammonium fluoride in THF at room temperature to yield the free nucleosides **(16)**, **(17)**, **(18)**, **(19)** and **(20)**(Figure 4). Attempts at deprotecting the pyrrolidine nitrogen function led to decomposition of the nucleoside in all cases. The thymine-containing 4'-*t*-butylcarbamyl nucleoside **(16)** was treated with 98% formic acid to remove the *t*-BOC group; however only free thymine was isolated from the mixture. Concern as to whether these harsh conditions were causing cleavage of the pseudoglycosidic bond led to the use of a non-acidic *t*-BOC deprotection agent. Trimethylsilyl iodide (TMS-I) is commonly used in peptide chemistry to remove the *t*-BOC group.[14] However addition of TMS-I to a solution of the thymidine analogue **7** also led to the liberation of thymine. The 4'-toluenesulphonamidyl thymidine analogue **(14)** was exposed to a solution of sodium naphthalenate[15] in an attempt to deprotect the nitrogen function. This again caused decomposition of the nucleoside. These results support the hypothesis that unprotected 4'-amino nucleosides are highly unstable, a property common to all geminal diamines.[16]

BIOLOGICAL TESTING

The results of *in-vitro* biological tests against herpes simplex virus type 1, herpes simplex virus type 2, varicella zoster virus, influenza virus, human immunodeficiency virus

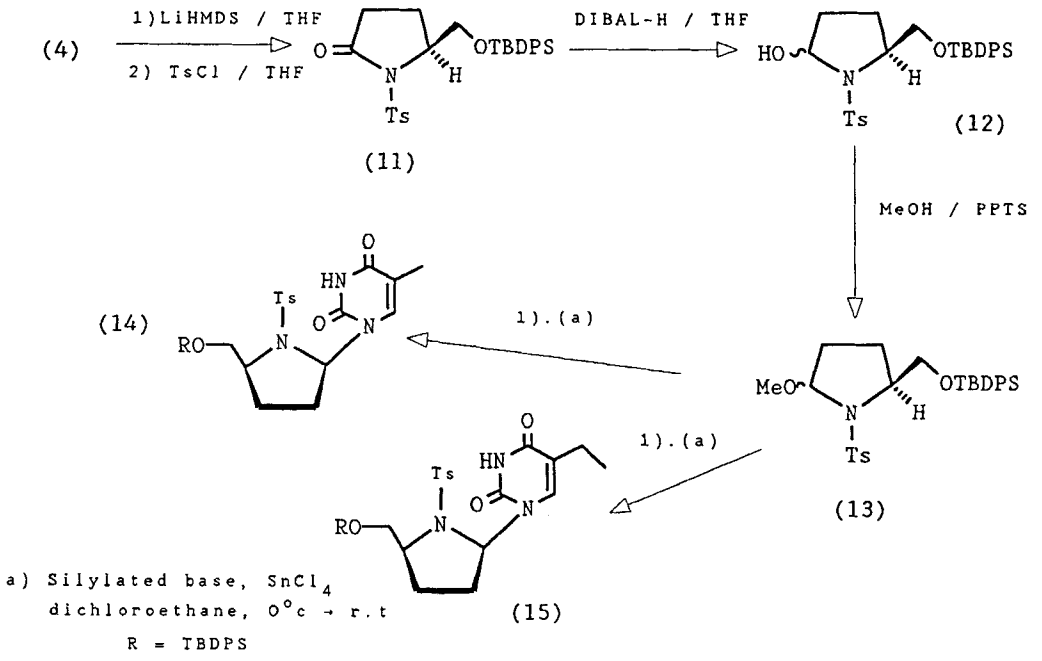

FIGURE 3

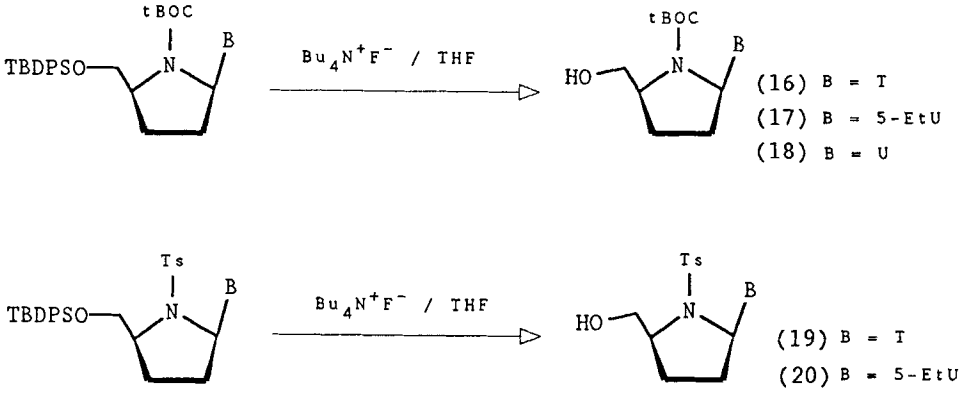

FIGURE 4

1# and human cytomegalovirus are tabulated below. None of the compounds tested showed any significant activity.

	HSV-1	HSV-2	VZV	Influenza	HIV-1	HCMV	$CCID_{50}$
16	>50	>50	>40	>100	>50	<100	>500
17	>100	>100	>40	>100	>100	>50	>500
18	>100	>100	>40	>100	>50	>100	>500
19	>100	>100	>40	>100	>5 T50	>100	135
20	>100	>100	>40	>100	>50 / S50	>100	488

S = slightly toxic, T = Toxic, All values are micromolar. # HIV-1 / CD4.

EXPERIMENTAL

Thin layer chromatography. Precoated, aluminium-backed silica gel plates were supplied by E.Merck A.G., Darmstadt, Germany. (silica gel 60 F_{254}, thickness 0.2mm). Development was by the ascending method. Detection was by quenching of fluorescence at 254nm and by adsorption of iodine vapour. **Column chromatography.** Glass columns were slurry packed in the chosen eluant under gravity with silica gel (Kieselgel 60, 70-250 mesh ASTM, type 7734 supplied by E.Merck A.G) Samples were applied to columns as solutions. **U.V.Spectroscopy.** Samples were dissolved in spectroscopic grade ethanol and spectra recorded on a Perkin-Elmer 552 spectrophotometer. **N.M.R Spectroscopy** ^{1}H-n.m.r spectra were recorded on Jeol GX-270 (270MHz), Bruker AC-300 (300MHz) and Bruker AMX-400 (400MHz) spectrometers. Variable temperature measurements were made on the AMX-400. All spectra were recorded relative to tetramethylsilane as the internal standard. **Mass Spectroscopy.** Spectra were recorded on a Kratos MS-80 mass spectrometer with a DS-55 data system or a Kratos MS-580RF mass spectrometer. Chemical ionisation methods (c.i) used NH_3 as carrier gas and fast atom bombardment (f.a.b) methods used 3-nitrobenzyl alcohol or glycerol as matrix, with sodium and potassium ion doping when necessary. **Elemental analysis.** Analyses were performed using a Perkin-Elmer 240 elemental analyser. **Melting points.** Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. **Solvents and reagents.** All solvents were dried and distilled according to standard procedures. Solid reagents were dried in a vacuum dessicator over phosphorous pentoxide. Liquid reagents were used as supplied without further purification.

(*S*)-(-)-2-Pyrrolidone-5-methylcarboxylate (2). To a cooled solution of (*S*)-(-)-2-pyrrolidone-5-carboxylic acid [(L)-pyroglutamic acid] (5.0 g, 38.7 mmol) in dry methanol

(75 ml), was added $SOCl_2$ (3.41 g, 28.7 mmol) dropwise with magnetic stirring. After stirring at room temperature for 2 hours the mixture was concentrated under vacuum to give a clear oil. Distillation of the oil (b.p 140-144°C / 4 mmHg) gave the pure product as a clear colourless oil (4.43 g, 80%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 6.84 (1 H, s, NH), 4.25 (1 H, m, H5), 3.75 (3 H, s, OCH_3), 2.5-2.1 (4 H, m, H3, H4); *m/z*: (f.a.b) 287 $(M_2)^+$, 144 $(M+H)^+$, (c.i) 144 $(M+H)^+$.

(*S*)-(-)-5-Hydroxymethyl-2-pyrrolidone (3). To a cooled solution of **2** (4.4 g,38.2 mmol) in dry ethanol was added powdered $NaBH_4$ (1.44 g, 38.2 mmol) in small portions. After stirring at room temperature for 2 hours, the mixture was acidified with concentrated HCl to approx. pH.1. The mixture was then filtered to remove inorganic salts, then concentrated under vacuum to give a cloudy oil. Column chromatography of the oil using 4:1 dichloromethane / methanol afforded the pure product as an oil which crystallised on standing (3.0 g, 85%). Mpt. 73-74°C. (^{1}H-n.m.r; 300 MHz,$CDCl_3$) 6.6 (1 H, s, NH), 3.8 (2 H, dd, C*H*$_2$OH), 3.45 (1 H, m, H5), 2.95 (1 H, s, OH), 2.4-1.6 (4 H, m, H3, H4); *m/z*: (c.i) 116 $(M+H)^+$. Found: C;52.24, H;7.88, N;12.45 $C_5H_9NO_2$ requires C;52.16, H;7.88, N;12.17.

(*S*)-(-)-5-Diphenyl*tert*-butylsilyloxymethyl-2-pyrrolidinone (4). To **3** in dry dichloromethane at 0°C was added imidazole (4.22 g, 62.02 mmol) and DMAP (0.5 g, 4.13 mmol). The resulting mixture was stirred for 30 minutes before adding *tert*-butyldiphenylsilylchloride dropwise over 10 minutes. The mixture was then stirred overnight at room temperature. The reaction was quenched by addition of water followed by separation of the organic phase. The aqueous phase was back extracted with dichloromethane and the combined organic extracts dried over magnesium sulphate. Concentration under vacuum gave a viscous oil which was purified by column chromatography (90:10 dichloromethane / methanol) to give the title compound as a clear oil which crystallised on standing (10.52 g, 72%). M.pt. 68-70°C. d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 7.7-7.3 (10 H, m, Ph_2Si), 5.85 (1 H, s, NH), 3.8 (1 H, m, H5), 3.65 (1 H, dd, C*H*$_2$OSi), 3.5 (1 H, dd, C*H*$_2$OSi), 2.4-1.6 (4 H, m, H3, H4), 1.05 (9 H, s, t-butyl); *m/z*: (c.i) 354 $(M+H)^+$. Found: C;71.25, H;7.75, N;3.93 $C_{21}H_{27}NO_2Si$ requires C;71.34, H;7.70, N;3.96.

(*S*)-(-)-N-*tert*-Butyloxycarbonyl(5-diphenylsilyl*tert*-butylsilyloxy-methyl)-2-pyrrolidone (5). To a solution of **4** (14.6 g, 41.3 mmol) in dry dichloromethane (100 ml) at 0°C was added triethylamine (6.27 g, 61.9 mmol) and DMAP (0.75 g, 6.19 mmol) with magnetic stirring. After 30 minutes a solution of di-*tert*-butyloxycarbonate (10.82 g, 49.5 mmol) in dichloromethane was added dropwise to the stirred, cooled solution. The mixture was then allowed to warm to room temperature and stirred for a further 18 hours. Isolation of the product was by acidification of the reaction mixture with

1M HCl, followed by separation of the organic layer. The organic extract was then washed with brine and water before drying over magnesium sulphate. Concentration of the extracts under vacuum gave a viscous oil which was chromatographed with chloroform-ethylacetate (80:20) to give the title compound as a white crystalline solid on removal of the solvent. (9.3 g, 50%). M.pt. 102-104°C d(^{1}H-n.m.r; 270 MHz,$CDCl_3$) 7.7-7.3 (10 H, m, Ph_2Si), 4.2 (1 H, m, H5), 3.9 (1 H, dd, CH_2OSi), 3.7 (1 H, dd, CH_2OSi), 2.9-2.0 (4 H, m, H3,H4), 1.45 (9 H, s, *t*-BOC), 1.05 (9 H, s, *t*-butyl); *m/z*: (f.a.b) 454 $(M+H)^+$. Found: C;68.5, H;7.7, N;3.3: $C_{26}H_{35}NO_4$ requires C;68.8, H;7.8, N;3.1.

N-*tert*-Butyloxycarbonyl(5-diphenyl*tert*-butylsilyloxy methyl)-2-hydroxypyrrolidine (6). To a solution of **5** (0.25 g, 0.55 mmol) in dry THF (50 ml) at -78°C under nitrogen gas was added lithium triethylborohydride (0.23 g, 2.2 mmol) as a 1molar solution in THF. On completion of the addition of the reducing agent, the reaction mixture was allowed to warm to room temperature. After 2 hours the reaction was quenched by addition of water and the resulting mixture extracted twice with dichloromethane. The organic extracts were dried over magnesium sulphate and concentrated under vacuum to give the title compound as a colourless syrup (0.26 g, 100%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 7.7-7.3 (10 H, m, Ph_2Si), 5.45 (1 H, m, H2), 4.1-3.5 (3 H, m, H5, CH_2OSi), 3.85 (1 H, s, OH), 2.4-1.8 (4 H, m, H3, H4), 1.5-1.35 (9 H, m, *t*-BOC), 1.05 (9 H, d, *t*-butyl); *m/z*: (c.i) 456 $(M-OH)^+$.

N-*tert*-Butyloxycarbonyl(5-diphenyl*tert*-butylsilyloxy methyl)-2-methoxypyrrolidine (8). To a solution of **(6)** (0.3 g, 0.65 mmol) in dry methanol at room temperature was added pyridinium *p*-toluenesulphonate (0.02 g, 0.06 mmol). The flask was firmly stoppered and stirred at room temperature for 18 hours. After this time the mixture was partitioned between dichloromethane / water, and the organic layer separated. Concentration of the organic layer under vacuum gave the title compound as a colourless oil (0.3 g, 100%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 7.7-7.3 (10 H, m, Ph_2Si), 5.5-5.1 (1 H, m, H2), 4.0-3.5 (3 H, m, H5, CH_2OSi), 3.5-3.2 (3 H, q, OCH_3), 2.4-1.6 (4 H, m, H3, H4), 1.5-1.35 (9 H, q,*t*-BOC), 1.05 (9 H,t ,*t*-butyl); *m/z*: (c.i) 456 $(M-OCH_3)^+$. Found: C;68.80, H;8.3, N;2.9 $C_{27}H_{39}NO_4Si$ requires C;69.04, H;8.37, N;2.98.

(*S*)-(-)-*p*-Toluenesulphonyl(5-diphenyl*tert*-butylsilyloxy methyl)-2-pyrrolidone (11). To the silyl-ether,**(4)** (5.0 g, 14.1 mmol) in dry THF (100 ml) at -20°C under nitrogen, was added lithium hexamethyldisilazide (2.83 g, 16.97 mmol) as a 1 molar solution in THF. The resulting mixture was stirred for 10 minutes at this temperature before quenching with a solution of *p*-toluenesulphonyl chloride (3.23 g, 16.9 mmol) in THF. Stirring was continued at room temperature for a further 60 minutes.

Water and dichloromethane were then added and the organic layer separated, washed with brine and then dried over magnesium sulphate. Concentration of the solution under vacuum gave a brown oil which was chromatographed initially with hexane-ethylacetate 80:20, and then hexane-ethylacetate 60:40. On evaporation of the appropriate fractions the title compound was obtained as large, clear crystals (5.38 g, 75%). M.pt. 114-116°C. d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 7.9 (2 H, d, $SO_2C_6H_4CH_3$), 7.7-7.3 (10 H, m, Ph_2Si), 7.25 (2 H, d, $SO_2C_6H_4CH_3$), 4.45 (1 H, m, H5), 4.1-3.7 (2 H, dd, CH_2OSi), 2.7 (1 H, m, H3), 2.4 (3 H, s, $SO_2C_6H_4CH_3$), 2.4-1.9 (3 H, m, H3, H4), 1.05 (9 H, s, *t*-butyl); *m/z*: (c.i) 508 $(M+H)^+$. Found: C;66.50, H;6.75, N;2.71 $C_{28}H_{33}NO_4SSi$ requires C;66.24, H;6.55, N;2.76.

N-*p*-Toluenesulphonyl(5-diphenyl*tert*-butylsilyloxy methyl)-2-hydroxypyrrolidine (12). Compound **11** (4.0 g, 7.9 mmol) was dissolved in dry THF (100 ml), the flask flushed with nitrogen gas and cooled to -78°C. Diisobutylaluminium hydride (2.24 g, 15.8 mmol) as a 1 molar solution in THF was then added slowly to the cooled mixture. After 2 hours stirring at room temperature the reaction mixture was poured into aqueous potassium sodium tartrate, and the resulting mixture extracted twice with dichloromethane. The organic extracts were dried over magnesium sulphate and concentrated under vacuum to give the product as a white foam (4.0 g, 99%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 7.9 (2 H, d, $SO_2C_6H_4CH_3$), 7.7-7.3 (10 H, m, Ph_2Si), 7.25 (2 H, d, $SO_2C_6H_4CH_3$), 5.5 (1 H, m, H2), 3.9-3.75 (2 H, dd, CH_2OSi), 3.7 (1 H, s, OH), 3.3 (1 H, m, H5), 2.4 (3 H, s, $SO_2C_6H_4CH_3$), 2.2-1.6 (4 H, m, H3, H4), 1.05 (9 H, s, *t*-butyl); *m/z*: (c.i) 429 $(M-OH)^+$. Found: C;66.27, H;7.11, N;2.91 $C_{28}H_{35}NO_4SSi$ requires C;65.98, H;6.92, N;2.91.

N-*p*-Toluenesulphonyl(5-diphenyl*tert*-butylsilyloxymethyl)-2-methoxypyrrolidine (13). Compound **12** (4.0 g, 7.85 mmol) was dissolved in dry methanol (100 ml) at room temperature. Pyridinium *p*-toluenesulphonate (0.39 g, 1.57 mmol) was then added to the solution and the resulting mixture stirred overnight. Isolation of the product was by addition of water / dichloromethane, followed by separation of the organic layer. The organic layer was then dried over magnesium sulphate and concentrated under vacuum to give the title compound as a pale yellow oil (3.69 g, 89%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 7.65 (4 H, m, Ph_2Si), 7.55 (2 H, d, $SO_2C_6H_4CH_3$), 7.4 (6 H, m, Ph_2Si), 7.25 (2 H, d, $SO_2C_6H_4CH_3$), 5.0 (1 H, d, H2), 4.1 (1 H, m, H5), 3.7-3.4 (2 H, m, CH_2OSi), 3.35 (3 H, s, OCH_3), 2.4 (3 H, s, $SO_2C_6H_4CH_3$), 2.2-1.6 (4 H, m, H3, H4), 1.05 (9 H, s, *t*-butyl); *m/z*: (c.i) 492 $(M-OH)^+$. Found: C;66.25, H;7.25, N;2.9 $C_{29}H_{37}NO_4SSi$ requires C;66.50, H;7.12, N;2.67.

Preparation of silylated bases; general procedure. To 1.0 g of dried, finely powdered pyrimidine base was added hexamethyldisilazane (8 ml) and trimethylsilyl

chloride (1ml). The resulting suspension was refluxed at 140°C, with exclusion of moisture, until complete dissolution of the pyrimidine had occurred. Removal of the silylating agents under high vacuum afforded the silylated base as an oil which was used immediatly without further purification.

Preparation of dideoxy pyrrolodine sugar nucleoside analogues; general procedure. The silylated pyrimidine prepared as above was sealed in a flask and flushed with dry nitrogen gas. A solution of **6**, **8** or **13** (1 molar equivalent) in dichloroethane was then added to the base and the mixture cooled to 0°C. To the cooled mixture, stannic chloride (1.1 molar equivalents) or TMS-triflate (1.1 molar equivalent) were added dropwise with stirring. The mixture was then allowed to warm to room temperature with stirring for a further 3 hours. After this time the reaction was quenched by addition of sodium hydrogen carbonate solution, and the mixture extracted and washed several times with dichloromethane and brine. The combined organic extracts were then dried over magnesium sulphate.

1-[N-*tert*-Butyloxycarbonyl(5-diphenyl*tert*-butylsilyloxy methyl)-pyrrolidin-2-yl]-5-methyluracil (7). 2,4-*bis*-*O*-(trimethylsilyl)thymine (0.28 g, 1.06 mmol) was treated with **8** (0.5 g, 1.06 mmol) in the presence of stannic chloride (0.3 g, 1.16 mmol) in accordance with the aforementioned procedure. Purification of the oil obtained, by column chromatography (chloroform-ethylacetate, 70:30), gave the title compound as a white foam after drying in a dessicator (0.16 g, 26%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.0 (1 H, s, N^3H), 7.7-7.3 (10 H, m, Ph_2Si), 6.1 (1 H, m, H2'), 4.3-3.7 (3 H, m, H5', CH_2OSi), 2.4-1.6 (4 H, m, H3', H4'), 1.5-1.35 (9 H, q, *t*-BOC), 1.2 (3 H, d, CH_3), 1.05 (9 H, m, *t*-butyl); *m/z*: (c.i) 565 $(M+H)^+$. λ_{max} 268 nm (e=6065). Accurate mass (e.i) $C_{31}H_{41}N_3O_5Si$ calculated for 563.7675 $(M)^+$ found 563.2742 $(M)^+$[17].

1-[N-*tert*-Butyloxycarbonyl(5-diphenyl*tert*-butylsilyloxy-methyl)-pyrrolidin-2-yl]-5-ethyluracil (9). 5-Ethyl-2,4-*bis*-*O*-(trimethylsilyl)uracil (0.30 g, 2.12 mmol) was treated with **8** (1.0 g, 2.12 mmol) in the presence of stannic chloride (0.60 g, 2.32 mmol) in accordance with the aforementioned procedure. Purification of the oil obtained, by column chromatography (chloroform-ethylacetate, 70:30), gave the title compound as an amorphous solid after drying (0.23 g, 18%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.0 (1 H, s, N^3H), 7.7-7.3 (10 H, m, Ph_2Si), 6.1 (1 H, m, H2'), 4.3-3.7 (3 H, m, H5', CH_2OSi), 2.4-1.6 (4 H, m, H3', H4'), 2.1 (2 H, q, CH_2CH_3), 1.5-1.35 (9 H, q, *t*-BOC), 1.1 (3 H, t, CH_2CH_3), 1.05 (9 H, t, *t*-butyl); *m/z*: (c.i) 578 $(M+H)^+$. λ_{max} 268 nm (e=5395).

1-[N-*tert*-Butyloxycarbonyl(5-diphenyl*tert*-butylsilyloxy methyl)-pyrrolidin-2-yl]uracil (10). 2,4-*bis*-*O*-(trimethylsilyl)uracil (3.38 mmol) was treated with **8** (1.54 g, 3.38 mmol) in the presence of stannic chloride (0.92 g, 3.72

mmol) in accordance with the aforementioned procedure. Purification of the oil obtained, by column chromatography (chloroform-ethylacetate, 70:30), gave the title compound as a white foam when dried under high vacuum (0.24 g, 13%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.5 (1 H, s, N^3H), 8.0 (1 H, s, H6), 7.7-7.3 (10 H, m, Ph_2Si), 6.15 (1 H, m, H2'), 5.3 (1 H, d, H5'), 4.5-3.7 (3 H, m, H5', CH_2OSi), 2.4-1.9 (4 H, m, H3', H4'), 1.5-1.35 (9 H, q, *t*-BOC), 1.05 (9 H, t, *t*-butyl); *m/z*: (f.a.b) 550 $(M+H)^+$, 572 $(M+Na)^+$. λ_{max} 262 nm (e=8618). Found: C;65.53, H;7.24, N;7.54 $C_{30}H_{39}N_3O_5Si$ requires C;65.54, H;7.15, N;7.64.

1-[N-*p*-Toluenesulphonyl(5-diphenyl*tert*-butylsilyloxy methyl)-pyrrolidin-2-yl]-5-methyluracil (14). 2,4-*bis*-*O*-(trimethylsilyl)thymine (1.19 mmol) was treated with **13** (1.0 g, 1.01 mmol) in the presence of stannic chloride (0.26 g, 1.01 mmol) in accordance with the aforementioned procedure. Purification of the oil obtained, by column chromatography (chloroform-ethylacetate, 60:40), gave the title compound as a white foam (0.85 g, 72%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.45 (1 H, s, N^3H), 7.75 (2 H, d, $SO_2C_6H_4CH_3$), 7.7 (4 H, m, Ph_2Si), 7.5 (1 H, s, H6), 7.4 (6 H, m, Ph_2), 7.35 (2 H, d, $SO_2C_6H_4CH_3$), 6.0 (1 H, t, H2'), 4.15 (1 H, m, H5'), 3.95-3.75 (2 H, m, CH_2OSi), 2.45 (3 H, s, $SO_2C_6H_4CH_3$), 2.2-1.5 (4 H, m, H3', H4'), 1.6 (3 H, s, CH_3), 1.05 (9 H, s, *t*-butyl); *m/z*: . λ_{max} 263 nm (e=9458). Found: C;62.40, H;6.21, N;6.50 $C_{32}H_{39}N_3O_5SSi$ requires C;62.20, H;6.36, N;6.80.

1-[N-*p*-Toluenesulphonyl(5-diphenyl*tert*-butylsilyloxy methyl)-pyrrolidin-2-yl]-5-ethyluracil (15). 5-Ethyl-2,4-*bis*-*O*-(trimethylsilyl)uracil (1.9 mmol) was treated with **13** (1.0 g, 1.9 mmol) in the presence of stannic chloride (0.54 g, 2.1 mmol) in accordance with the aforementioned procedure. Purification of the oil obtained, by column chromatography (chloroform-ethylacetate, 70:30), gave the title compound as a white foam (0.63 g, 54%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.2 (1 H, s, N^3H), 7.8 (2 H, d, $SO_2C_6H_4CH_3$), 7.7-7.3 (10 H, m, Ph_2Si), 7.35 (2 H, d, $SO_2C_6H_4CH_3$), 6.0 (1 H, t, H2'), 4.0-3.8 (3 H, m, H5', CH_2OSi), 2.4 (3 H, s, $SO_2C_6H_4CH_3$), 2.1 (2 H, q, CH_2CH_3), 2.0-1.1 (4 H, m, H3', H4'), 1.05 (9 H, s, *t*-butyl), 0.95 (3 H, t, CH_2CH_3); *m/z*: (f.a.b) 632 $(M+H)^+$. λ_{max} 263 nm (e=7740). Found: C;64.65, H;6.53, N;6.63 $C_{34}H_{41}N_3O_5SSi$ requires C;64.63, H;6.54, N;6.65.

Removal of *tert*-butyldiphenylsilyl protecting group; general procedure. To a nucleoside analogue protected as the *tert*-butyldiphenylsilyl ether in dry THF at room temperature was added an excess (3 molar equivalents) of tetrabutylammonium fluoride. The resulting solution was then stirred for 3 hours at room temperature after which time water and dichloromethane were added. The organic layer was then separated, dried over magnesium sulphate and concentrated under vacuum. The crude deprotected nucleoside

analogue was obtained as an oil which was purified by column chromatography (chloroform-ethanol, 90:10).

1-[N-*tert*-Butyloxycarbonyl(5-hydroxymethyl)pyrrolidin-2-yl]-5-methyluracil (16). Compound **7** (0.16 g, 0.03 mmol) was treated according to the deprotection conditions described above. The deprotected, purified nucleoside analogue was obtained as an amorphous solid (100%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.4 (1 H, s, N^3H), 7.6 (1 H, s, H6), 4.3-3.5 (3 H, m, H5', CH_2OH), 2.3-1.6 (4 H, m, H3', H4'), 1.9 (3 H, s, CH_3), 1.5-1.35 (9 H, q, *t*-BOC); *m/z*: (f.a.b) 200 (M-thymine)$^+$. λ_{max} 269 nm (e=7240).

1-[N-*tert*-Butyloxycarbonyl(5-hydroxymethyl)pyrrolidin-2-yl]-5-ethyluracil (17). Compound **10** (0.20 g, 0.03 mmol), was treated according to the deprotection conditions described above. The deprotected, purified nucleoside analogue was obtained as a white foam (0.12 g, 98%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.5 (1 H, s, N^3H), 7.55-6.8 (1 H, d, H6), 6.1 (1 H, m, H2'), 4.4-3.4 (3 H, m, H5', CH_2OH), 2.5 (2 H, q, CH_2CH_3), 2.4-1.6 (4 H, m, H3', H4'), 1.5-1.35 (9 H, q, *t*-BOC), 1.15 (3 H, t, CH_2CH_3); *m/z*: (c.i) 340 (M+H)$^+$. λ_{max} 268 nm (e=5400). Accurate mass (e.i) $C_{11}H_{16}N_3O_3$ (M-*t*BOC)$^+$ calculated for 238.2657 (M-*t*BOC)$^+$ found 238.1190 (M-*t*BOC)$^+$[17].

1-[N-*tert*-Butyloxycarbonyl(5-hydroxymethyl)pyrrolidin-2-yl]uracil (18). Compound **9** (0.22 g, 0.4 mmol) was treated according to the deprotection conditions described above. The deprotected, purified nucleoside analogue was obtained as a white amorphous powder (0.10 g, 90%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.85 (1 H, s, N^3H), 7.8 (1 H, d, H6), 6.15 (1 H, m, H2'), 5.75 (1 H, d, H5), 4.2-3.7 (3 H, m, H5', CH_2OH), 2.5-1.8 (4 H, m, H3', H4'), 1.5-1.35 (9 H, q, *t*-BOC); *m/z*: (f.a.b) 312 (M+H)$^+$ λ_{max} 262 nm (e=9083). Found: C;53.99, H;7.01, N;13.20 $C_{14}H_{21}N_3O_5$ requires C;54.01, H;6.80, N;13.50.

1-[N-*p*-Toluenesulphonyl(5-hydroxymethyl)pyrrolidin-2-yl]-5-methyluracil (19). Compound **14** (0.27 g, 0.44 mmol) was treated according to the deprotection procedure described above. The deprotected, purified nucleoside analogue was obtained as a white foam (0.15 g, 91%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.7 (1 H, s, N^3H), 7.8 (2 H, d, $SO_2C_6H_6CH_3$), 7.7 (1 H, s, H6), 7.4 (2 H, d, $SO_2C_6H_6CH_3$), 6.0 (1 H, t, H2'), 4.15 (1 H, m, H5'), 3.8 (2 H, m, CH_2OH), 2.65 (1 H, s, OH), 2.4 (3 H, s, $SO_2C_6H_6CH_3$), 2.2-1.6 (4 H, m, H3', H4'), 1.9 (3 H, s, CH_3); *m/z*: (f.a.b) 380 (M+H)$^+$. λ_{max} 263 nm (e=6930). Found: C;53.61, H;5.30, N;10.77 $C_{17}H_{21}N_3O_5S$ requires C;53.81, H;5.58, N;11.07.

1-[N-*p*-Toluenesulphonyl(5-hydroxymethyl)pyrrolidin-2-yl]-5-ethyluracil (20). Compound **15** (0.5 g, 0.79 mmol) was treated according to the deprotection

procedure described above. The deprotected, purified nucleoside analogue was obtained as a white foam (0.3 g, 97%). d(^{1}H-n.m.r; 300 MHz,$CDCl_3$) 8.4 (1 H, s, N^3H), 7.8 (2 H, d, $SO_2C_6H_4CH_3$), 7.7 (1 H, s, H6), 7.35 (2 H, d, $SO_2C_6H_4CH_3$), 6.0 (1 H, t, H2'), 4.15 (1 H, m, H5'), 3.8 (2 H, m, CH_2OH), 2.4 (3 H, s, $SO_2C_6H_4CH_3$), 2.4-1.5 (4 H, m, H3', H4'), 2.10 (2 H, q, CH_2CH_3), 1.15 (3 H, t, CH_2CH_3); *m/z:* (f.a.b) 394 $(M+H)^+$. Found: C;54.84, H;5.69, N;10.45 $C_{18}H_{23}N_3O_5S$ requires C;55.09, H;5.91, N;10.71.

ACKNOWLEDGEMENTS

The authors thank Dr G.W.Hardy and Dr M.Slater for their assistance with this project. Thanks are also due to SERC and the Wellcome Foundation Ltd. for providing a CASE award to L.P.

REFERENCES

1) D.W.Norbeck, S.Spanton, S.Broder, H.Mitsuya, Tetrahedron Lett., 1989,**46**,6263. C.K.Chu, S.K.Ahn, H.O.Kim, J.W.Beach, A.J.Alves, L.S.Jeong, Q.Islam, P.Van Roey, R.F.Schinazi, Tetrahedron Lett., 1991,**32**,3791 H.O.Kim, K.Shanmuganathan, A.J.Alves, L.S.Jeong, J.W.Beach, R.F.Schinazi, C.-N.Chang, Y.-C.Cheng, C.K.Chu, Tetrahedron Lett., 1992,**33**,6899.

2) J.A.Secrist, K.N.Tiwari, J.M.Riordan, J.A.Montgomery, J.Med.Chem., 1991,**34**,2361. M.R.Dyson, P.L.Coe, R.T.Walker, J.Med.Chem., 1991,**34**,2782.

3) B.Belleau, D.Dixit, N.Nguyen-Ba, J.L.Kraus, Abstracts of papers, 5th International Conference on AIDS, Montreal 1989. Abstract No.TCO1. C.K.Chu, J.W.Beach, L.S.Jeong, B.G.Choi, F.I.Comer, A.J.Alves, R.F.Schinazi, J.Org.Chem., 1991,**56**,6503.

4) M.R.Harnden, R.L.Jarvest, Tetrahedron Lett., 1991,**32**,1991. M.R.Harnden, R.L.Jarvest, J.Chem.Soc.Perkin Trans.1, 1991,9. M.R.Harnden, R.L.Jarvest, M.J.Parrat, J.Chem.Soc.Perkin Trans.1, 1992,2259.

5) F.M.Kaspersen, U.K.Pandit, J.Chem.Soc.Perkin Trans.1, 1976,1617. F.M.Kaspersen, U.K.Pandit, J.Chem.Soc.Perkin Trans.1, 1976,1798. F.M.Kaspersen, H.Bieraugel, U.K.Pandit, Heterocycles, 1974,**2**,15. K.E.Ng, L.E.Orgel, J.Med.Chem., 1989,**32**,1754. M.L.Peterson, R.Vince, J.Med.Chem. 1991,**34**,2787.

6) E.J.Reist, D.E.Gueffroy, R.W.Blackford, L.Goodman, J.Org.Chem., 1966,**31**,4025. E.J.Reist, L.V.Fisher, L.Goodman, J.Am.Chem.Soc., 1967,**32**,2541. G.D.Kini, W.J.Hennen, J.Org.Chem., 1986,**51**,4436.

7) H.Mitsuya, S.Broder, Proc.Natl.Acad.Sci.USA., 1986,**83**,1911.

8) B.Huang, B.Chen, Y.Hui, Synthesis 1993,769.

9) S.Saijo, M.Wada, J.-I.Himizu, A.Ishida, Chem.Pharm.Bull., 1980,**28**,1449.

10) K.Woo, K.Jones, Tetrahedron Lett., 1991,**32**,47.

11) W.Speckamp, H.Hiemstra, Tetrahedron, 1985,**41**,4367.

12) J.Ahman, P.Somfai, Tetrahedron, 1992,**48**,9537.

13) J.Ahman, P.Somfai, Tetrahedron, 1992,**33**,3791.

14) R.S.Lott, V.S.Chauhan, C.H.Stammer, J.Chem.Soc.Chem.Commun., 1979,495.

15) S.Ji, L.B.Gortler, A.Waring, A.Battisti, S.Bank, W.D.Closson, P.Wriede, J.Am.Chem.Soc., 1967,**89**,5311. H.C.Jarrell, R.G.S.Ritchie, W.A.Szarek, J.K.N.Jones, Can.J.Chem., 1973,**51**,1767.

16) G.Moad, S.J.Benkovic, J.Am.Chem.Soc., 1978,**100**,5495.

17) Elemental analysis on these compounds failed to give a result within the acceptable error range. Accurate mass measurements were performed as a substitute for elemental analysis.

Received 11/23/93
Accepted 1/12/94