Stereoselective synthesis of novel 1′-substituted 2′-deoxy-4-thionucleosides

Alisdair C. MacCulloch, Paul L. Coe * and (the late) Richard T. Walker

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, UK B15 2TT

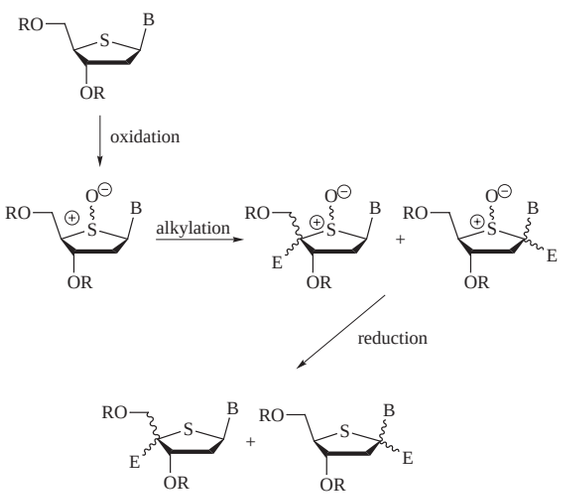
Received (in Cambridge) 5th October 1998, Accepted 10th December 1998

Oxidation of 2′-deoxy-5-ethyl-4-thiouridine with sodium metaperiodate afforded a separable mixture of (*R*)- and (*S*)-sulfoxides. These were converted, after protection as their *tert*-butyldimethylsilyl ethers, by reaction with LDA to the 1′-anion which was reacted with a number of electrophiles to furnish a range of novel nucleoside analogues. Deprotection of the (*R*)-sulfoxide of 2′-deoxy-5-ethyl-1′-methyl-4′-thiouridine with triethylamine–trihydrogen fluoride under very mild conditions gave the unprotected sulfoxide.

Introduction

Recently we[1,2] and others[3] have reported the synthesis of a novel series of nucleoside analogues, the 2′-deoxy-4-thionucleosides. Some of these have shown potent antiviral activity[4] and have been investigated for use in structural sudies[5] and in antisense[6] and antigene therapy.[7] The syntheses have generally manipulated normal sugars to provide their thio counterparts, the exception being the elegant synthesis devised by Uenishi which starts from readily available acyclic precursors.[8] However to date the vast majority of the 4′-thio analogues synthesised have been modified either in the base moiety or in the 2′ or 3′ positions. Within the Birmingham group we have been investigating the oxidised forms of the thio compounds, in particular the sulfoxides and sulfones, as potential intermediates for the synthesis of novel nucleosides.

Most of the chemistry of sulfones and sulfoxides we have studied involves the formation of carbanions at the position α to the sulfone. Most carbanionic reactions that have been reported are on sulfones and sulfoxides that are part of non-nucleoside structures. Treatment of a sulfone with base removes a proton to form the carbanion, which can then be treated with an electrophile to introduce a new group α to the sulfur atom. Generally, these reactions are carried out on structures with only one α-proton site next to the sulfur preventing additional products being formed. In the case of the oxidised 4′-thionucleosides a problem exists in that both positions α to the sulfur have protons available. We have been unable to reduce the sulfones back to the sulfides. We have therefore chosen to investigate the use of the derived sulfoxides as precursors for the preparation of new nucleoside analogues. The synthetic scheme envisaged is outlined in Scheme 1. We have recently reported[9] some related studies involving the deuteration of the unblocked sulfoxides **2** and **3** (Scheme 2) using sodium deuteroxide in D_2O. We found that deprotonation took place exclusively at the 4′-position and that some epimerisation occurred leading to a mixture of two deuterated diastereoisomers: **2** and **3** both reacted, as would be expected, in the same manner. Clearly we could not use this base system in attempts to functionalise the ring system so we blocked the free hydroxy groups as their *tert*-butyldimethylsilyl ethers. Selective alkylation of nucleosides at the 6-position in the base moiety has been reported by Tanaka[10] using LDA as the base at low temperatures but even so we chose to use this system as a first try with the sulfoxides.

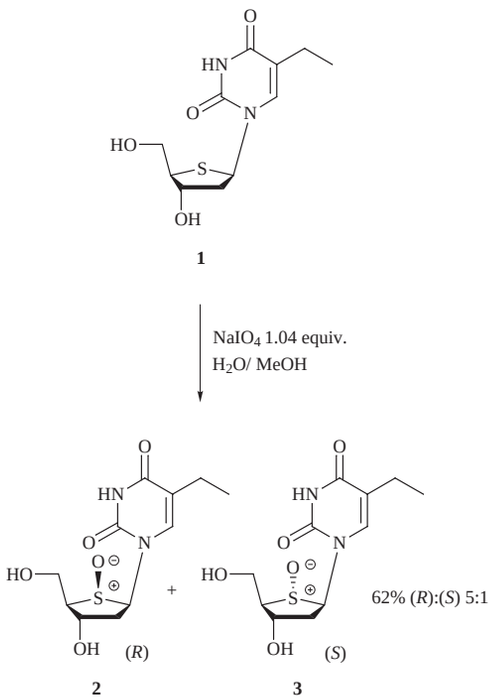


Scheme 1

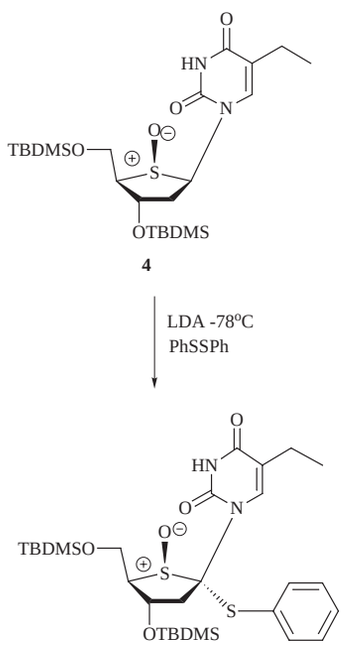
Results and discussion

The starting point for our synthesis was the potent antiherpes virus agent 2′-deoxy-5-ethyl-4′-thiouridine (5ETdU) (**1**), which had been synthesised as described.[1,2] This was oxidised and separated as shown in Scheme 2 as previously described[9] to afford the desired sulfoxides **2** and **3**. These were protected in the standard manner to yield the silyl ethers **4** and **5**. These latter were fully characterised by standard physical methods (see Experimental section).

The protected (*R*)-sulfoxide **4** was allowed to react with freshly prepared LDA (2.75 equiv.) for 2 hours at −78 °C before diphenyl disulfide (2 equiv.) was added. The reaction mixture was maintained at −78 °C for 18 hours before quenching with acetic acid and warming to room temperature. Purification and characterisation revealed that the reaction had occurred regioselectively at the C-1′ position. The initial identification of the product was based on the ^{1}H NMR data which clearly showed the absence of the signal for the anomeric proton (at C-1′) which in **4** appeared at δ 6.08–6.01 and the presence of the proton at C-4′ at δ 3.27–3.18. This is in contrast to the previous result we reported for the deuteration reaction.[9] Hence the only product (in addition to recovered starting material) was the (*R*)-sulfoxide of 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-ethyl-4′-thio-1′-phenylthio-β-uridine **6** (54%) (Scheme 3).



Scheme 2



Scheme 3

It is envisaged that the bulky protecting groups prevent the attack of the bulky base LDA at the now sterically hindered 4′ proton thereby preventing alkylations from taking place at the C-4′ position. Thus, the apparently less reactive proton (as evidenced by the deuteration studies[9]) at position C-1′ now reacts preferentially. As there was no longer a distinguishing anomeric proton signal visible in the ^{1}H NMR spectrum it was possible that the reaction had proceeded with epimerisation at the C-1′ position. Since only β-nucleosides usually are found to have biological activity, it was important to confirm that the reaction had occurred with retention of configuration. Crystallisation of the product from dichloromethane afforded crystals which were satisfactory for X-ray crystallographic analysis (for the method of X-ray analysis see Experimental section) which clearly showed that the reaction had occurred without epimerisation as shown in Fig. 1.

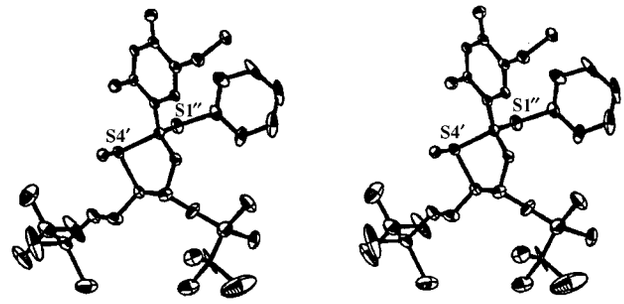


Fig. 1

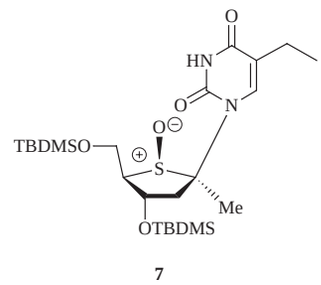
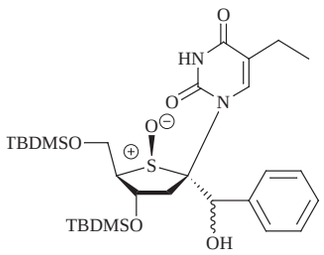


Fig. 2

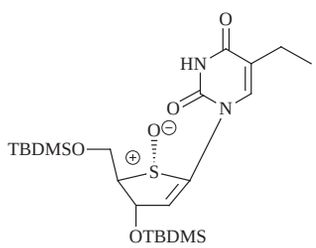
The reaction was then repeated using iodomethane as the electrophile which provided the desired 1′-methyl derivative **7** in a disappointingly low yield (9.6%) and starting material (70%). It was found that there were traces of the α-anomer in the recovered starting material. This suggested that the lithiation was successfully occurring but that the methylation was relatively slow resulting in some epimerisation at the anomeric carbon atom. The low yield compared to the *S*-phenyl derivative was attributed to the decreased electrophilicity of the iodomethane compared to diphenyl disulfide. In order to overcome this the reaction was repeated using 10 equiv. of iodomethane and a longer reaction time (30 hours). This provided the 1′-methyl derivative **7** (Fig. 2) in a yield of 68% with no other product being observed by any of the chromatographic techniques we used. From the spectroscopic evidence we cannot conclusively say that the product is all of the β or the α anomer and unlike the phenylthio derivative **6** we were unable to crystallise the product. Unfortunately we also were unable to carry out NOE experiments which might have been able to confirm the structure. We therefore at this stage have to rely on analogy to suggest that this and compound **8** (see below) are like **6** and are both β anomers. We repeated this and the other reactions we have described for sulfoxide **6** with its diastereoisomer **5** derived from the (*S*)-sulfoxide **3** and obtained the corresponding derivatives.

The protected sulfoxides were also reacted with two other types of electrophiles in order to confirm that a range of nucleoside analogues could be synthesised. Reacting the (*R*)-sulfoxide **4** with benzaldehyde (4 equiv.) using the same conditions and purification by column chromatography furnished a diastereoisomeric mixture of (*R*)-sulfoxide **8** as a colourless gum (58% yield) (Fig. 3). However when the (*S*)-sulfoxide **5** nucleoside was reacted with iodine, instead of the 1′-substituted nucleoside being isolated, the 1′,2′-didehydro analogue **9** was obtained as a yellow solid (48%) (Fig. 4). This suggests that the 1′-iodinated compound is formed but spontaneously eliminates HI to form the didehydro compound. In the oxo sugar field these nucleoside analogues have been synthesised before[11] but are extremely unstable resulting in their immediate decomposition if deprotected. The (*R*)-sulfoxide of the 1′-methyl derivative **7** was reacted using standard tetrabutylammonium fluoride (TBAF) conditions for the removal of TBDMS groups, but only degradation products were isolated. This was probably due to the fluoride ion being too nucleophilic and attacking the



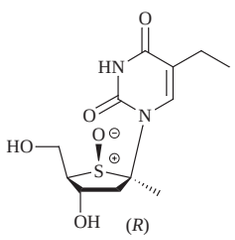
8

Fig. 3



9

Fig. 4



10

Fig. 5

C-4′ proton after removal of the silyl ethers. Hence a milder deprotection reagent was sought.

Triethylamine–3HF has been reported as a superior reagent than TBAF for the removal of silyl protecting groups from RNA.[12] When reacted for 20 hours at room temperature on compound **7** the deprotected 1′-methyl sulfoxide **10** (Fig. 5) was isolated in a yield of 82%. Biological testing of the compounds we have prepared is ongoing and the results will be reported later.

Experimental

General

NMR spectra were recorded using a Bruker AC300 spectrometer. ^{13}C NMR spectra were run as ^{13}C PENDANT NMR spectra. Mass spectra were obtained using a VG ZabSpec mass spectrometer. Chromatography was performed on Kieselgel 60, 70–250 mesh ASTM, supplied by E. Merck AG.

(*R*)- and (*S*)-Sulfoxides of 2′-deoxy-5-ethyl-4′-thiouridine (2 and 3)

To a stirred solution of 2′-deoxy-5-ethyl-4′-thiouridine **1** (498 mg, 1.83 mmol) in distilled water (20 ml) and methanol (20 ml) at 0 °C was added a 0.05 M aqueous solution of sodium metaperiodate (38 ml, 1.90 mmol). The reaction mixture was then left to warm to room temperature overnight before the product was purified by column chromatography (SiO_2, dichloromethane–methanol, 6:1, v/v) to yield (i) the (*R*)-sulfoxide **2** (271 mg, 51.3%) as a gum (Found: C, 45.6; H, 5.8; N, 9.7; S, 11.0%. $C_{11}H_{16}N_2O_5S$ requires: C, 45.8; H, 5.6; N, 9.7; S, 11.1%); δ_H (DMSO-d_6) 11.50 (1H, s, NH), 7.35 (1H, s, H-6), 5.96–5.88 (1H, dd, ^3J 8.0, 10.0, H-1′), 5.50–5.47 (1H, d, ^3J 5.0, 3′-OH), 5.14–5.09 (1H, t, ^3J 4.5, 5′-OH), 4.32–4.23 (1H, m, H-3′), 3.82–3.68 (2H, m, H-5′), 3.20–3.13 (1H, m, H-4′), 2.76–2.66, 2.33–2.25 (2H, m, H-2′), 2.27–2.18 (2H, q, ^3J 8.0, CH_2CH_3), 1.04–0.98 (3H, t, ^3J 8.0, CH_2CH_3); δ_C (DMSO-d_6) 163.16 (C-4), 150.82 (C-2), 137.60 (C-6), 114.16 (C-5), 71.01 (C-3′), 70.86 (C-1′), 68.25 (C-4′), 55.88 (C-5′), 35.94 (C-2′), 19.93 (CH_2CH_3), 13.42 (CH_2CH_3); ((+ve) FAB) *m*/*z* 311 (100%, $[M + Na]^+$), 289 (25%, $[M + H]^+$); and (ii) the (*S*)-sulfoxide **3** (57 mg, 10.7%) as a gum (Found: C, 45.6; H, 5.5; N, 9.5%. $C_{11}H_{16}N_2O_5S$ requires: C, 45.8; H, 5.6; N, 9.7%); δ_H (DMSO-d_6) 11.50 (1H, s, NH), 7.64–7.59 (1H, s, H-6), 5.75–5.67 (1H, dd, ^3J 8.0, 11.0, H-1′), 5.63–5.56 (1H, d, ^3J 4.0, 3′-OH), 5.42–5.38 (1H, t, ^3J 5.0, 5′-OH), 4.33–4.27 (1H, m, H-3′), 3.89–3.69 (2H, m, H-5′), 3.09–3.01 (1H, m, H-4′), 2.54–2.43, 2.36–2.25 (2H, m, H-2′), 2.27–2.18 (2H, q, ^3J 8.0, CH_2CH_3), 1.07–1.01 (3H, t, ^3J 8.0, CH_2CH_3); δ_C (DMSO-d_6) 163.32 (C-4), 150.53 (C-2), 138.2 (C-6), 115.9 (C-5), 82.59 (C-3′), 78.23 (C-1′), 70.66 (C-4′), 58.44 (C-5′), 37.00 (C-2′), 19.64 (CH_2CH_3), 13.10 (CH_2CH_3); ((+ve) FAB) *m*/*z* 311 (100%, $[M + Na]^+$), 289 (20%, $[M + H]^+$).

(*R*)- and (*S*)-Sulfoxides of 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-ethyl-4′-thio-β-uridine (4 and 5)

To a stirred diastereoisomeric mixture of compounds **2** and **3** (2.05 g, 7.12 mmol) in dry DMF (10 ml) was added imidazole (1.55 g, 22.78 mmol), dimethylaminopyridine (173.98 mg, 1.42 mmol) and *tert*-butyldimethylsilyl chloride (3.22 g, 21.36 mmol) and the resulting mixture stirred at room temperature for 48 hours. The reaction mixture was then washed with brine (100 ml), the organic layer was dried ($MgSO_4$), concentrated *in vacuo* and redissolved in ethyl acetate, and then purified by column chromatography (SiO_2, *n*-hexane–ethyl acetate 3:2 v/v) to yield (i) the (*R*)-sulfoxide **4** (1.98 g, 79%) as a white foam (Found: C, 53.8; H, 8.8; N, 5.3; S, 6.0%. $C_{23}H_{44}N_2O_5SSi_2$ requires: C, 53.5; H, 8.5; N, 5.4; S, 6.2%); δ_H ($CDCl_3$) 9.92–9.87 (1H, br s, NH), 7.24–7.22 (1H, s, H-6), 6.08–6.01 (1H, dd, ^3J 6.6, 12.2, H-1′), 4.93–4.86 (1H, m, H-3′), 4.05–3.81 (2H, m, H-5′), 3.27–3.18 (1H, m, H-4′), 2.87–2.75 (1H, m, H-2′), 2.30–2.22 (3H, q, H-2′, ^3J 7.7, CH_2CH_3), 1.09–1.03 (3H, t, ^3J 7.7, CH_2CH_3), 0.84–0.79 (18H, 2 × s, 2 × $C(CH_3)_3$), 0.05–0.02 (12H, s, $SiCH_3$); δ_C ($CDCl_3$) 163.28 (C-4), 150.87 (C-2), 135.92 (C-6), 116.55 (C-5), 72.74 (C-3′), 71.24 (C-1′), 68.39 (C-4′), 57.60 (C-5′), 36.70 (C-2′), 25.64, 25.49 (2 × $C(CH_3)_3$), 20.09 (CH_2CH_3), 18.08, 17.67 (2 × $C(CH_3)_3$), 12.67 (CH_2CH_3), −4.99, −5.62 (2 × $SiCH_3$); ((+ve) FAB) *m*/*z* 561 (100%, $[M + 2Na]^+$), 539 (75%, $[M + Na]^+$); and (ii) the (*S*)-sulfoxide **5** (0.92 g, 79%) as a white foam (Found: C, 53.3; H, 8.7; N, 5.1; S, 6.1%. $C_{23}H_{44}N_2O_5SSi_2$ requires: C, 53.5; H, 8.5; N, 5.4; S, 6.2%); δ_H ($CDCl_3$,) 9.92–9.89 (1H, s, N-H), 7.12–7.00 (1H, s, H-6), 5.51–5.44 (1H, m, H-1′), 4.61–4.56 (1H, m, H-3′), 4.05–3.87 (2H, m, H-5′), 3.28–3.21 (1H, m, H-4′), 2.74–2.62 (1H, m, H-2′), 2.38–2.27 (1H, m, H-2′, CH_2CH_3), 1.13–1.07 (3H, m, CH_2CH_3), 0.89–0.85 (18H, 2 × s, 2 × $C(CH_3)_3$), 0.08–0.05 (12H, 2 × s, 4 × $SiCH_3$); δ_C ($CDCl_3$) 163.75 (C-4), 150.22 (C-2), 138.86 (C-6), 117.35 (C-5), 86.75 (C-3′), 78.54 (C-1′), 72.19 (C-4′), 59.45 (C-5′), 38.05 (C-2′), 25.83, 25.70 (2 × $C(CH_3)_3$), 20.03 (CH_2CH_3), 18.25, 17.94 (2 × $C(CH_3)_3$), 12.62 (CH_2CH_3), −4.79, −5.41 (2 × $SiCH_3$); ((+ve) FAB) *m*/*z* 561 (25%, $[M + 2Na]^+$), 539 (100%, $[M + Na]^+$).

(*R*)-Sulfoxide of 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-ethyl-1′-phenylthio-4′-thio-β-uridine (6)

The method described here is illustrative. To a stirred solution of freshly distilled diisopropylamine (DIPA) (418 ml, 2.99 mmol) in dry THF (10 ml) at −90 °C under a stream of argon was added butyllithium (2.5 M in hexane) (1.32 ml, 3.29 mmol) keeping the temperature below −80 °C. The resulting mixture was stirred for 2 hours, allowing complete formation of the LDA. A solution of compound **4** (617 mg, 1.20 mmol) in THF

(25 ml) was then syringed into the mixture maintaining a temperature of below −70 °C. After 2 hours diphenyl disulfide (522 mg, 2.39 mmol) in THF (10 ml) was added to the reaction mixture which was left stirring for 18 hours, using a Cryostat to maintain the temperature at *ca.* −70 °C, before being quenched with glacial acetic acid (1 ml) and left to warm to room temperature. The reaction mixture was then concentrated *in vacuo*, redissolved in dichloromethane (30 ml), washed with aqueous sodium bicarbonate solution (30 ml), dried ($MgSO_4$) concentrated *in vacuo* and purified by column chromatography (SiO_2, hexane–ethyl acetate 2:1 v/v) to yield compound **6** as a yellow gum (400 mg, 54%). Recrystallisation from dichloromethane with slow evaporation of the solvent afforded some crystals suitable for X-ray analysis (Found: C, 54.6; H, 7.3; N, 4.3; S, 9.9%. $C_{29}H_{48}N_2O_5S_2Si_2$ requires: C, 54.3; H, 7.5; N, 4.4; S, 10.0%); δ_H ($CDCl_3$) 9.24–9.20 (1H, s, NH), 7.46–7.21 (5H, m, S*Ar*), 6.71–6.68 (1H, br s, H-6), 4.44–4.38 (1H, m, H-3′), 4.14–3.93 (3H, m, H-4′, H-5′), 3.36–3.25, 3.12–2.98 (2H, m, H-2′), 2.10–2.01 (2H, q, CH_2CH$_3$), 0.94–0.87 (18H, 2 × s, 2 × C(CH_3)$_3$), 0.85–0.78 (3H, t, CH$_2$CH_3), 0.13–0.05 (12H, 4 × s, 4 × SiCH_3); δ_C ($CDCl_3$) 162.90 (C-4), 149.61 (C-2), 137.86 (C-Ar), 131.01 (C-6), 129.45 (C-Ar), 127.85 (C-Ar), 115.43 (C-5), 92.27 (C-1′), 73.10 (C-3′), 69.83 (C-4′), 58.37 (C-5′), 46.09 (C-2′), 25.91, 25.71 (2 × C(*C*H$_3$)$_3$), 19.94 (*C*H$_2$CH$_3$), 18.37, 17.89 (2 × *C*(CH$_3$)$_3$), 12.77 (CH$_2$*C*H$_3$), −4.52, −4.88 (2 × Si*C*H$_3$); ((+ve) FAB) *m*/*z* 669 (35%, [M + 2Na]$^+$), 647 (100%, [M + Na]$^+$), 625 (5%, [M + H]$^+$).

(*S*)-Sulfoxide of 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-ethyl-4′-thio-1′-thiophenyl-β-uridine (6a)

In a similar experiment to the above but using the (*S*)-sulfoxide **5** (317 mg, 0.61 mmol) and diphenyl disulfide (268 mg, 1.23 mmol) we obtained the sulfoxide **6a** (199 mg, 52%) as a yellow gum, δ_H ($CDCl_3$) 8.79–8.74 (1H, s, NH), 7.42–7.26 (5H, m, ArH), 6.71–6.68 (1H, s, H-6), 4.44 (1H, m, H-3′), 4.29–4.40, 4.04–3.96 (H, m, H-5′), 2.91–2.82 (1H, m, H-4′), 2.68–2.63 (1H, m, H-2′), 2.33–2.21 (3H, m, H-2′, CH_2CH$_3$), 1.06–1.0 (3H, t, ^3J 7.3, CH$_2$CH_3), 0.94–0.82 (18H, 2 × s, 2 × C(CH$_3$)$_3$); (+ve FAB), *m*/*z* 669 [M + 2Na]$^+$, 646 [M + Na]$^+$, 625 [M + H]$^+$.

(*R*)-Sulfoxide of 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-ethyl-1′-methyl-4′-thio-β-uridine (7)

Using the method outlined above, DIPA (239 ml, 1.71 mmol) was reacted with butyllithium (2.5 M in hexane) (752 ml, 1.88 mmol) in THF (40 ml). After 2 hours a solution of compound **4** (353 mg, 0.684 mmol) in THF (5 ml) was added through a syringe. After 2 hours iodomethane (433 ml, 6.84 mmol) was added by syringe, and the resulting reaction mixture left stirring for 30 hours. Work up was carried out using the standard conditions before purification by column chromatography (SiO_2, hexane–ethyl acetate 3:2 v/v) yielded compound **7** as a colourless gum (251 mg, 68%) (Found: C, 54.3; H, 9.0; N, 5.0; S, 5.9%. $C_{24}H_{46}N_2O_5SSi_2$ requires: C, 54.4; H, 8.7; N, 5.3; S, 6.1%); δ_H ($CDCl_3$) 9.68–9.62 (1H, s, NH), 6.92–6.88 (1H, s, H-6), 4.28–4.22 (1H, m, H-3′), 4.06–3.73 (2H, m, H-5′), 3.29–3.17 (1H, m, H-4′), 2.98–2.87 (1H, m, H-2′), 2.34–2.26 (3H, m, H-2′, CH_2CH$_3$), 1.80–1.77 (3H, s, CH$_3$), 1.10–1.02 (3H, t, ^3J 7.3, CH$_2$CH_3), 0.86–0.82 (18H, 2 × s, 2 × C(CH_3)$_3$), 0.08–0.04 (12H, 2 × s, 2 × SiCH_3); δ_C ($CDCl_3$) 163.46 (C-4), 150.32 (C-2), 136.56 (C-6), 116.73 (C-5), 85.03 (C-1′), 72.29 (C-3′), 70.73 (C-4′), 58.52 (C-5′), 44.12 (C-2′), 25.92, 25.62 (2 × C(*C*H$_3$)$_3$), 21.04 (CH$_3$), 20.55 (*C*H$_2$CH$_3$), 18.40, 17.76 (2 × *C*(CH$_3$)$_3$), 12.93 (CH$_2$*C*H$_3$), −4.55, −4.70 (2 × Si*C*H$_3$); ((+ve) FAB) *m*/*z* 575 (25%, [M + 2Na]$^+$), 553 (100%, [M + Na]$^+$) (25%, [M + H]$^+$).

(*R*)-Sulfoxide of 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-5-ethyl-1′-phenyl(hydroxy)methyl-4′-thio-β-uridine (8)

Using the method outlined above, DIPA (446 ml, 3.19 mmol) was reacted with butyllithium (1.40 ml, 3.56 mmol) in THF (20 ml). After 2 hours a solution of compound **4** (470 mg, 0.91 mmol) in THF (5 ml) was added by syringe. After 2 h benzaldehyde (369 ml, 3.64 mmol) was added by syringe. After 24 h the reaction was quenched with glacial acetic acid (1 ml). Work up was carried out using the standard conditions before purification by column chromatography (SiO_2, hexane–ethyl acetate 3:2 v/v) which yielded **8** as a colourless gum (301 mg, 58%) (Found: C, 57.7; H, 8.0; N, 4.6; S, 5.3%. $C_{30}H_{50}N_2O_6SSi_2$ requires: C, 57.8; H, 8.1; N, 4.5; S, 5.2%); δ_H ($CDCl_3$) 10.09–10.04, 9.48–9.45 (1H, s, NH), 7.32–7.11 (5H, m, Ar-H), 6.56–6.53, 6.07–6.04 (1H, s, H-6), 5.94–5.90, 5.38–5.33 (1H, m, ArC*H*(OH)), 4.98–4.90 (1H, m, ArCH(O*H*)), 4.98–4.90, 4.39–4.33 (1H, m, H-3′), 4.16–3.88 (2H, m, H-5′), 3.24–2.90 (1H, m, H-4′), 2.98–2.91, 2.48–2.23 (1H, m, H-2′), 1.95–1.83 (2H, m, CH_2CH$_3$), 0.89–0.85 (21H, m, 2 × C(CH_3)$_3$, CH$_2$CH_3), 0.12–0.06 (12H, 2 × s, 4 × SiCH_3); δ_C ($CDCl_3$) 163.28, 163.06 (C-4), 151.23 (C-2), 141.01, 138.01 (Ar-C), 138.94, 136.18 (C-6), 128.55, 128.45, 127.44, 127.00 (Ar-C), 116.18, 115.03 (C-5), 91.41, 86.32 (C-1′), 73.74 (C-3′), 71.13 (C-4′), 70.64, 68.77 (ArCH(OH)), 57.75, 57.43 (C-5′), 40.14 (C-2′), 25.91, 25.65 (2 × C(*C*H$_3$)$_3$), 20.10, 19.95 (*C*H$_2$CH$_3$), 18.35, 17.87 (2 × *C*(CH$_3$)$_3$), 13.03, 12.19 (CH$_2$*C*H$_3$), −4.47, −5.37 (2 × Si*C*H$_3$); ((+ve) FAB) *m*/*z* 667 (60%, [M + 2Na]$^+$), 645 (100%, [M + Na]$^+$).

(*R*)-Sulfoxide of 3′,5′-di-*O*-(*tert*-butyldimethylsilyl)-2′-deoxy-1′,2′-didehydro-5-ethyl-4′-thio-β-uridine (9)

Using the method outlined above DIPA (373 ml, 2.67 mmol) was reacted with butyllithium (2.5 M in hexane) (1.18 ml, 2.93 mmol) in THF (40 ml) After 2 hours a solution of compound **6** (550 mg, 1.07 mmol) in THF (5 ml) was added by syringe. After 2 hours iodine (541 mg, 2.13 mmol) in THF (5 ml) was added by syringe. After 24 hours the reaction was quenched with glacial acetic acid (1 ml). Work up was carried out using the standard conditions before purification by column chromatography (SiO_2, hexane–ethyl acetate 3:2 v/v) yielded compound **9** as a yellow solid (264 mg, 48%) (Found: C, 53.4; H, 8.4; N, 5.3; S, 6.1%. $C_{23}H_{42}N_2O_5S_1Si_2$ requires C, 53.7; H, 8.2; N, 5.4; S, 6.2%); δ_H ($CDCl_3$) 11.74–11.71 (1H, s, NH), 7.52–7.49 (1H, s, H-6), 6.80–6.77 (1H, d, ^3J 2.2, H-2′), 5.10–5.06 (1H, m, H-3′), 4.12–3.86 (2H, m, H-5′), 3.09–3.01 (1H, m, H-4′), 2.37–2.20 (2H, q, ^3J 7.4, CH_2CH$_3$), 1.10–1.00 (3H, t, ^3J 7.4, CH$_2$CH_3), 0.89–0.85 (18H, 2 × s, 2 × C(CH_3)$_3$), 0.12–0.06 (12H, 2 × s, 4 × SiCH_3); δ_C ($CDCl_3$) 163.53 (C-4), 149.31 (C-2), 146.04 (C-1′), 139.45 (C-6), 135.98 (C-2′), 116.73 (C-5), 74.87 (C-3′), 73.84 (C-4′), 51.22 (C-5′), 25.92, 25.62 (2 × C(*C*H$_3$)$_3$), 25.83, 25.69 (2 × *C*(CH$_3$)$_3$), 19.61 (*C*H$_2$CH$_3$), 13.02 (CH$_2$*C*H$_3$), −3.07 (2 × Si*C*H$_3$); ((+ve) FAB) *m*/*z* 559 (100%, [M + 2Na]$^+$), 537 (65%, [M + Na]$^+$).

(*R*)-Sulfoxide of 2′-deoxy-5-ethyl-1′-methyl-4′-thio-β-uridine (10)

To a sample of compound **7** (270 mg, 0.51 mmol) dissolved in dichloromethane (10 ml) was added triethylamine–3HF (170 μl, 1.20 mmol). The resulting solution was stirred for 20 hours when examination (TLC, dichloromethane–methanol 8:1 v/v) showed the absence of starting material. Purification by column chromatography (SiO_2, dichloromethane–methanol 8:1 v/v) furnished compound **10** as a white foam (127 mg, 82%) (Analysis as the sodium salt: Found: C, 44.96; H, 6.32; N, 8.51%. $C_{12}H_{18}N_2O_5SNa$ requires C, 44.30; H, 5.58; N, 8.61%); δ_H (DMSO-d_6) 11.45 (1H, s, NH), 7.39 (1H, s, H-6), 5.59–5.53 (1H, d, ^3J 5.0, 3′-OH), 5.14–5.07 (1H, t, ^3J 4.5, 5′-OH), 4.13–4.04 (1H, m, H-3′), 3.82–3.68 (2H, m, H-5′), 2.81–2.70 (1H, m, H-4′), 2.52–2.40, 1.54–1.48 (2H, m, H-2′), 2.25–2.18 (2H, q, ^3J 8.0, CH_2CH$_3$), 1.68 (3H, s, CH$_3$), 1.05–0.98 (3H, t, ^3J 8.0, CH$_2$CH_3); δ_C (DMSO-d_6) 163.20 (C-4), 150.71 (C-2), 138.41 (C-6), 114.69 (C-5), 84.29 (C-1′), 70.20 (C-3′), 69.51 (C-4′), 56.50 (C-5′),

43.12 (C-2′), 20.43 (CH_3), 19.78 (CH_2CH_3), 13.24 (CH_2CH_3); $C_{12}H_{18}N_2O_5SNa$ requires 325.0833; found 325.0834.

X-Ray structural determination data for compound 6 (Fig. 1)

A single crystal was mounted in the diffractometer. Data were collected using a Rigaku R axis II area detector refractometer using graphite monochromated Mo-Kα radiation. The structure was determined by direct methods[13,14] and refined on F^2 by least squares using anisotropic displacement parameters for non-hydrogen atoms. Hydrogen atoms were placed in calculated positions with isotropic displacement parameters. The figure depicted was prepared using ORTEP.

Crystal data and refinement. Formula: $C_{29}H_{48}N_2O_6S_2Si_2$. $M = 640.99$. Crystal system triclinic, unit cell dimensions $a = 17.894(2)$, $b = 18.712(2)$, $c = 11.284(10)$ Å. $\alpha = 94.877(4)$, $\beta = 90.085(9)$, $\gamma = 103.542(7)°$. $V = 3659.2(6)$ Å^3. $\lambda = 0.71069$ Å. $T = 293$ K. Space group $P\bar{1}$ (no. 1). $Z = 4$. $D_c = 1.164$ mg m^{-3}. μ 0.240 mm^{-1}. Crystal size 0.50 × 0.30 × 0.25 mm. $F(000)$ 1376. θ range for data collection 1.42–21.93°. Index ranges $-18 \leqslant h \leqslant 18$, $-19 \leqslant k \leqslant 9$, $-11 \leqslant l \leqslant 11$. Reflections collected 12969. Independent reflections 11858 [R(int) = 0.0368]. Refinement method: full-matrix least-squares on F^2. Data/restraints/parameters 11858/2/1417. Goodness-of-fit on F^2 1.079. Final R indices [I.2$\sigma(I)$] $R_1 = 0.0958$, $wR = 0.2666$. R indices all data. $R_1 = 0.1018$, $wR_2 = 0.2771$. $w = [\Sigma^2(F_o^2) + (0.17P)^2 + 4.20P]$; $P = (F_o^2 + 2F_c^2)/3$. Flack parameter −0.04(13). Largest diff. peak and hole 0.0904 and −0.445 e Å^{-3}.†

† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/290.

References

1 M. R. Dyson, P. L. Coe and R. T. Walker, *Carbohydr. Res.*, 1991, **216**, 237.
2 M. R. Dyson, P. L. Coe and R. T. Walker, *J. Med. Chem.*, 1991, **34**, 2782.
3 J. A. Secrist, K. N. Tiwari, J. M. Riodan and J. A. Montgomery, *J. Med. Chem.*, 1991, **34**, 2361.
4 S. G. Rahim, N. Trivedi, M. V. Bogunovic-Batchelor, G. W. Hardy, G. Mills, J. W. T. Selway, W. Snowden, E. Littler, P. L. Coe, I. Basnak, R. F. Whale and R. T. Walker, *J. Med. Chem.*, 1996, **39**, 789; N. A. Van Draanen, G. A. Freeman, S. A. Short, R. Harvey, R. Jansen, G. Szczech and G. W. Koszalka, *J. Med. Chem.*, 1996, **39**, 538; R. T. Walker, *Anti-infectives: Recent Advances in Chemistry and Structure Activity Relationships*, eds. P. H. Bentley and P. J. O'Hanlon, Royal Society of Chemistry, Cambridge, 1997, pp. 203–237.
5 L. H. Koole, J. Plavec, H. Lui, B. R. Vincent, M. R. Dyson, P. L. Coe, R. T. Walker, G. W. Hardy, S. G. Rahim and J. Chattopadhyaya, *J. Am. Chem. Soc.*, 1992, **114**, 9936; D. F. Ewing and G. MacKenzie, *Nucleosides, Nucleotides*, 1996, **15**, 809.
6 T. J. Boggon, E. L. Hancox, K. E. McAuley-Hecht, B. A. Connolly, W. N. Hunter, T. Brown, R. T. Walker and G. A. Leonard, *Nucleic Acids Res.*, 1996, **24**, 951; E. L. Hancox, B. A. Connolly and R. T. Walker, *Nucleic Acids Res.*, 1993, **21**, 3485; G. D. Jones, E. A. Lesnik, S. R. Owens, L. M. Risen and R. T. Walker, *Nucleic Acids Res.*, 1996, **24**, 4117; S. Kumar, J. R. Horton, G. D. Jones, R. T. Walker, R. J. Roberts and X. Cheng, *Nucleic Acids Res.*, 1997, **25**, 2773.
7 G. D. Jones, K.-H. Altmann, D. Hüsken and R. T. Walker, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 1275.
8 J. Uenishi, M. Motoyama, Y. Nishiyama and S. Wakabayashi, *J. Chem. Soc.*, *Chem. Commun.*, 1991, 1421.
9 A. C. MacCulloch and R. T. Walker, *Tetrahedron*, 1998, **54**, 12457.
10 H. Tanaka, H. Hayakawa and T. Miyasaka, *Chem. Pharm. Bull.*, 1981, **29**, 3565; H. Tanaka, H. Hayakawa and T. Miyasaka, *Tetrahedron*, 1982, **38**, 2635; H. Hayakawa, H. Tanaka, K. Obi, M. Ito and T. Miyasaka, *Tetrahedron Lett.*, 1987, **28**, 87.
11 M. J. Robins and E. M. Trip, *Tetrahedron Lett.*, 1974, **15**, 3369; M. J. Robins and R. A. Jones, *J. Org. Chem.*, 1974, **39**, 113; Y. Yoshimura, F. Kano, N. Miyasaki, S. Sakata, K. Haraguchi, Y. Itoh, H. Tanaka and T. Miyasaka, *Nucleosides, Nucleotides*, 1996, **15**, 305.
12 E. Westman and R. Strömberg, *Nucleic Acids Res.*, 1994, **22**, 2430.
13 Molecular Structure Corp. TEXSAN Single Crystal Structure Analysis Software, version 1.6, MSC 3200 Research, Forest Drive TX 77381 USA, 1993.
14 G. M. Sheldrick, SHELXL-93 Program for Crystal Structure Refinement, University of Gottingen, 1993.

Paper 8/07721E