4′-Thionucleosides *via in Situ* Pyranose–Furanose Rearrangements: A Short Synthesis of the Antiherpes Agent 2′-Deoxy-5-ethyl-4′-thiouridine *via* Direct Coupling of a Silylated Pyrimidine Base with a 4-Thiopyranose Sugar

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Methyl 2-deoxy-3,4-*O*-thiocarbonyl-β-D-ribopyranoside was converted into the thione carbonate by reaction with thiophosgene. Bromide ion-catalyzed O–S rearrangement produced methyl 2-deoxy-3-*O*,4-*S*-carbonyl-4-thio-β-D-ribopyranoside (**3a**) and the 3-*O*,4-*S* isomer **3b**. The carbonates were cleaved with ammonia and the 3-*O*,4-*S* pyranoside sugar coupled with bis(trimethylsilyl)-5-ethyluracil using trimethylsilyl triflate to provide the antiherpes agent 2′-deoxy-5-ethyl-4′-thiouridine **9**. The reaction proceeded *via in situ* pyranoside rearrangement of the sugar and subsequent coupling. The pyranoside sugar could also be converted to the furanoside form with Dowex H^+ acid resin and coupled in conventional fashion to give the nucleoside. Coupling of methyl 4-*O*-carbamoyl-2-deoxy-3-thio-β-D-ribopyranoside (**4b**) with the bis(trimethylsilyl)-5-ethyluracil gave 1-[2-[2-(hydroxymethyl)thiiran-1-yl]-1-methoxyethyl]-5-ethyluracil.

Introduction

4′-Thionucleosides have received some attention in recent years mostly because of the reported anti-HIV activity[1] of the 2′,3′-dideoxy analogues. Several syntheses of both the D- and L-2′-deoxynucleosides have been reported[2] including *de novo* approaches[2a,2c] as well as methodology starting from carbohydrate precursors.[2b,d–f] Some conformational studies on 4′-thio-2′-deoxythymidine and (*E*)-5-(2-bromovinyl)-2′-deoxy-4′-thiouridine sought to relate the X-ray and solution conformations.[3] More recently other workers have reported the antiherpes activity of some 5-substituted pyrimidine analogues including the potent broad spectrum activity of 2′-deoxy-5-ethyl-4′-thiouridine[4] **9** (Scheme 2). We sought a direct and simple route to these molecules which avoided the use of large quantities of thiol reagents and consecutive double inversion of the stereochemistry at the 4′ position.

Our starting point for this work was the observation that 4-thiopyranoses could be produced from thiocarbonates by radical induced rearrangement,[5] thus achieving the required double inversion in a single synthetic step. A pyranose–furanose rearrangement, which has been reported for 4-thiohexoses,[6] would then provide the required 4-thiofuranoside which could be coupled with the silated pyrimidine base.

Results and Discussion

From 2-deoxy-D-ribose we readily prepared the β-anomer of the methyl pyranoside[7] **1** using a simplified form of the published procedure. The thiocarbonyl derivative **2** was then synthesized using either thiophosgene[8] or thiocarbonyl diimidazole.[9] Initially we encountered difficulties with the O–S rearrangment. Reaction using radical conditions generally gave low yields of **3a** and **3b**. After many trials we decided on the use of bromide ion to effect the rearrangement *via* a halide catalyzed double S_N2 inversion process (Scheme 1). This type of rearrangment has previously been reported for 1,2-cyclic thione carbonates.[8] A systematic study of this reaction was carried out varying the anion, cation, and solvent. We eventually settled on the use of tetrabutylammonium bromide in diglyme under reflux as offering the best compromise between the ratio of **3a** to **3b**, chemical yield, and the ease of carrying out the process. Unfortunately this reaction always gave an unfavorable ratio of 4-thio to 3-thio isomers. The isomers **3a** and **3b** could be separated by ammonolysis and flash chromatography of the carbamates. We were now able to follow through our original plan i.e. acid-catalyzed rearrangement to the furanose sugar **5** followed by toluoyl ester protection to **6**, coupling, and deprotection to give the desired 4′-thionucleoside **9** (Scheme 2). It was also possible to

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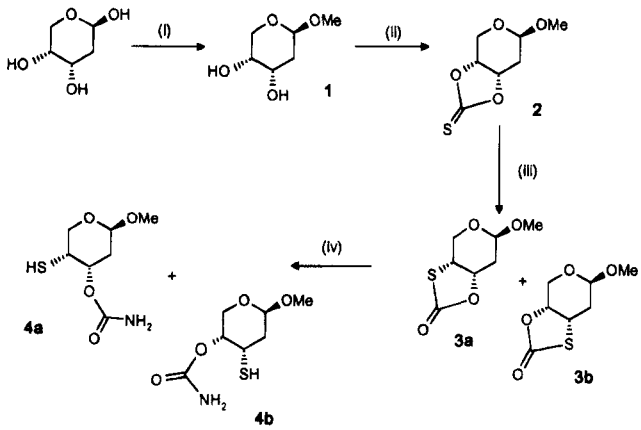
Scheme 1. Synthesis of 3- and 4-Thiopyranose Sugars[a]



[a] Reagents: (i) 1% HCl/MeOH, (ii) $CSCl_2$, (iii) $^tBu_4N^+Br^-$/diglyme/150 °C, (iv) NH_3/MeOH.

prepare **8** directly from **5a** *via in situ* protection of the sugar as its TMS ether (Scheme 2). However, as the pyranose–furanose rearrangement itself requires acid or Lewis acid catalysis the possibility of carrying out the coupling in a single operation was investigated. Treatment of the *in situ* silylated pyranose **4a** with trimethylsilyl triflate and silylated 5-ethyluracil provided the furanose nucleoside directly, presumably *via* ring opening, rearrangement, and subsequent generation of the thionium ion (Scheme 3). The α and β 3'-*O*-carbamoyl nucleosides **8** were the only products in 47% isolated yield. To our knowledge this is the only example of *in situ* rearrangement and direct coupling of a 4-thiofuranose sugar. A single example in the oxygen series was reported in one of a classic series of papers by Vorbruggen;[10] however, the sugar used was a mixture of furanose and pyranose forms and the extent of participation of the pyranose form in the reaction could not be ascertained. Intriguingly our decision to use *in situ*-silated pyranose sugar for the coupling proved critical as the protection of the thiol group as a toluoyl ester gave mostly pyranoside nucleosides on coupling, as evidenced by NMR of the complex reaction products. In a final trial we subjected the 3-thio isomer **4b** to the same conditions and obtained a low yield of the thiirane **10** as the major product (Scheme 4). In this case formation of the thiirane being favored over cyclization to form a thietane sugar or thietane nucleoside. The structure of **10** was determined by a combination of 2D COSY and ^{13}C DEPT NMR studies. The precise mechanism of the formation of the thiiarane nucleoside is not known. However, ring opening and attack of the base, followed by thiirane formation seems most likely, as the thiol and carbamate groups could adopt an antiperiplanar arrangement favoring elimination. We were also able to effect nucleoside formation by direct coupling of the unprotected furanoside **5** again using *in situ* protection as the trimethylsilyl ethers.

In conclusion we have developed a short convenient route to 4-thioribopyranoside and furanoside sugars. Such methodology may have wider application in the synthesis of nucleosides.

Experimental Section

Melting points are uncorrected. Flash chromatography was carried out by the method of Still[11] except that the columns were slurry packed. Merck silica art. no. 9385 was used. NMR spectra were run at 200 MHz unless otherwise indicated. Chemical shifts are in ppm relative to TMS. Acetonitrile (CH_3CN) was dried and distilled over calcium hydride prior to use. Solutions of bis(trimethylsilyl)-5-ethyluracil were prepared by refluxing 5-ethyluracil in excess hexamethyldisilazane (HMDS) containing a crystal of ammonium sulfate for 4 h, removing the excess reagent on a rotary evaporator (1 mm), and then dissolving the residue in CH_3CN. The phrase "workup gave" signifies that the product was washed with water and dried over Na_2SO_4 and the solvent removed on a rotary evaporator.

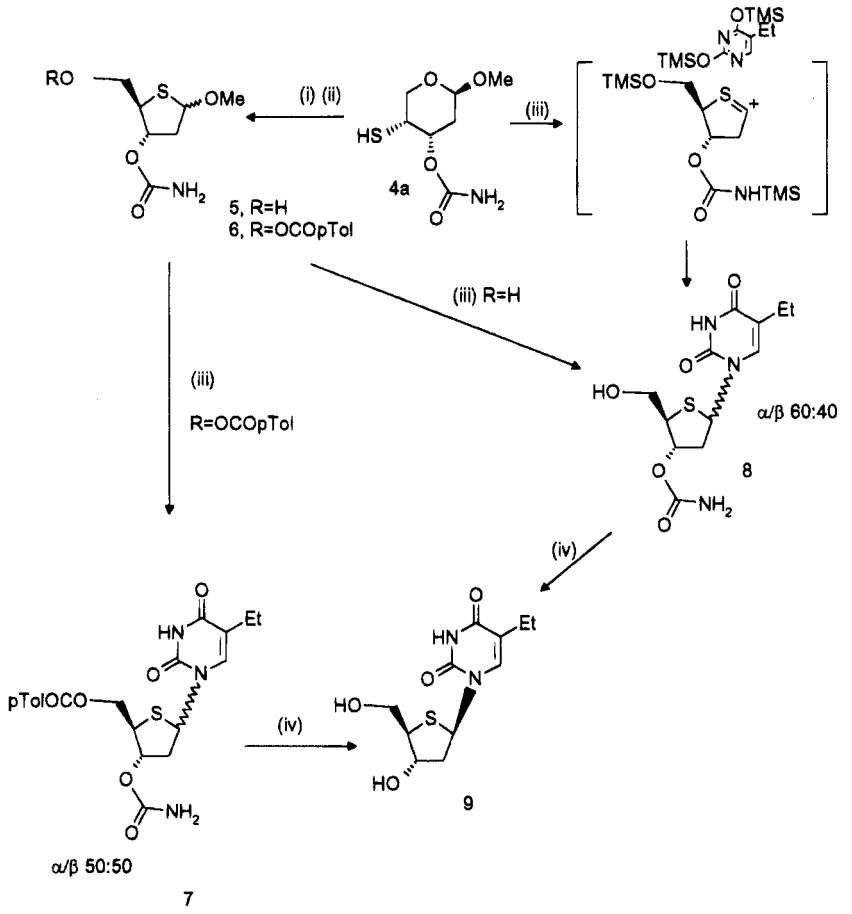
Methyl 2-Deoxy-β-D-ribopyranoside (1). To a solution of 1% concd HCl (75 mL) in methanol (MeOH) (2.5 L) was added 2-deoxy-D-ribose (530 g, 3.95 mol), and the mixture was stirred for 15 h at room temperature. The mixture was neutralized to pH 7 with solid $NaHCO_3$, stirred for 2 h, and then filtered, and the MeOH was removed under reduced pressure to give an oil. The oil was taken up into ethyl acetate (EtOAc) (1.2 L) and ether (3 L) and filtered to remove residual $NaHCO_3$. The filtrate was cooled to 8 °C when the product crystallized to give the β-anomer **1** (92.55 g, 0.62 mol, 16%) as a white solid. Mp 80–81 °C (lit.[14] 83.5 °C). ^1H NMR (200 MHz, $CDCl_3$) ppm 1.86 (1H, d, J = 3 Hz), 1.91 (1H, dd, J = 2 Hz and J = 3 Hz), 2.31 (1H, d, J = 7 Hz), 2.48 (1H, d, J = 5 Hz), 3.35 (3H, s), 3.75 (3H, m), 4.05 (1H, m), 4.77 (1H, t, J = 3 Hz). MS (FAB) m/z 149 (M + 1), 117, 99. This material was ~90% pure by NMR the residue being α anomer and furanoside forms. Further cooling of the filtrate gave a second crop (219.15 g ~80% pure β anomer).

Methyl 2-Deoxy-3,4-*O*-thiocarbonyl-β-D-ribopyranoside (2). Method A. To **1** (33.51 g, 0.226 mol) in dichloromethane (CH_2Cl_2) (500 mL) was added 4-(dimethylamino)-pyridine (63.5 g, 0.52 mol) followed by dropwise addition of thiophosgene (27.3 mL, 0.249 mol) maintaining a temperature of 0–10 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was cooled to 10 °C, and water was added. After stirring for 40 min, the mixture was extracted with CH_2Cl_2, workup gave **2** (37.3 g, 0.196 mmol 87%). Mp 106–108 °C. ^1H NMR (200 MHz, $CDCl_3$) ppm 1.9 (1H, ddd, J = 16 Hz, 6 Hz, 4 Hz), 2.45 (1H, dt, J = 16 Hz, 5 Hz), 3.4 (3H, s), 3.93 (2H, m), 4.88 (2H, m), 5.15 (1H, m). MS (FAB) m/z 191 (M^+ + 1), 159, 131, 113 (100%). Anal. $C_7H_{10}O_4S$ requires C 44.21%, H 5.26%. Found C 44.16%, H 5.30%.

Methyl 2-Deoxy-3,4-*O*-thiocarbonyl-β-D-ribopyranoside (2). Method B. To a solution of the **1** (14.8 g, 0.1 mol) in tetrahydrofuran (THF) (100 mL) heated at reflux was added a slurry of thiocarbonyldiimidazole in THF (50 mL). On cooling, the THF was removed under reduced pressure, the residue was taken up into EtOAc (200 mL) and washed with 3% HCl in brine (100 mL), and workup gave **2** (16.73 g, 88%).

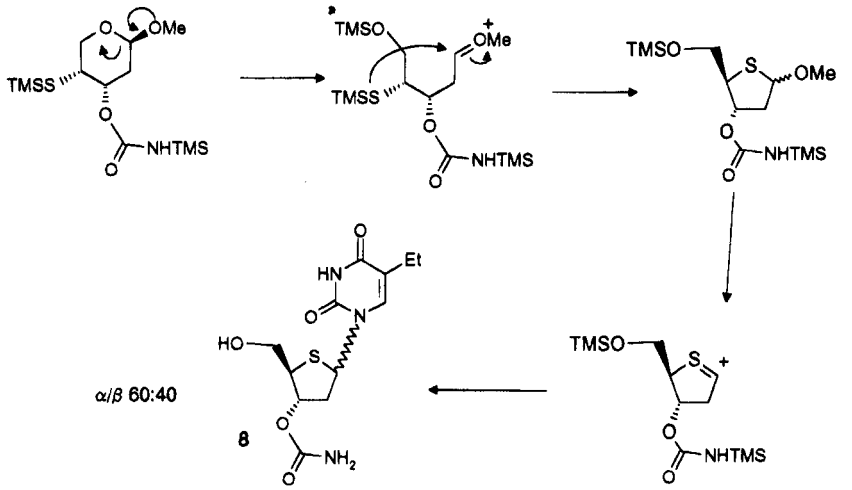
Methyl 2-Deoxy-3-*O*,4-*S*-carbonyl-4-thio-β-D-ribopyranoside (3a) and Methyl 2-Deoxy-4-*O*,3-*S*-carbonyl-4-thio-β-D-ribopyranoside (3b). To **2** (16.7 g, 88 mmol) in diglyme (167 mL) was added tetrabutylammonium bromide (14.61 g, 43.9 mmol), and the reaction was heated under reflux for 6 h. Another portion (14.16 g, 43.9 mmol) of tetrabutylammonium bromide was added, and the reaction heated under reflux for a further 3 h. The diglyme was removed under reduced pressure and the residue taken up in EtOAc. Workup gave an oil (19.45 g) containing a mixture of **3a** and **3b**. The oil was dissolved in ether and cooled to 0 °C. The crystallized **3b** isomer was filtered (4 g), and the filtrate was concentrated and distilled using a short vigreux column at 110–115 °C to give **3a** (6.59 g) containing 40% of **3b**. Compound **3a** could be purified by column chromatography (CH_2Cl_2 as eluant) if desired. **3a:** ^1H NMR (200 MHz, $CDCl_3$) ppm 1.97 (1H, ddd, J = 15 Hz, 7 Hz, 5 Hz), 2.4 (1H, ddd, J = 15 Hz, 5 Hz, 3 Hz), 3.4 (3H, s), 3.71 (1H, dd, J = 12.5 and 7 Hz), 3.93 (1H, m), 4.16 (1H, dd, J = 12.8 Hz, 4.8 Hz), 4.71 (1H, dd, J = 6.8 Hz, 3.25 Hz), 4.93 (1H, dd, J = 10 Hz, 5.3 Hz). MS (FAB) m/z 91 (M + 1), 149, 159, 113. IR (film) cm^{-1} 2962, 2937, 1736, 1072. $C_7H_{10}O_4S$ requires C 44.2%, H 5.26%, found C 43.91%, H 5.37%. **3b:** ^1H NMR (200 MHz, $CDCl_3$) ppm 2.04 (1H, ddd, J = 10.5 Hz, 7.5 Hz, 3.3 Hz), 2.21 (1H, ddd, J = 14 Hz, 4 Hz, 2.3 Hz), 3.38 (3H, s), 3.94 (1H, dd, J = 11.3 Hz, 2.5 Hz), 4.00 (1H, m), 4.13 (1H, dd, J = 13.5 Hz, 1.3 Hz), 4.49 (1H, m), 4.75 (1H, t, J = 2.3 Hz). MS (FAB) m/z 191 (M + 1), 159, 113. IR

Scheme 2. '-Thiouridines from Furanose and Pyranose Sugars[a]



[a] Reagents: (i) Dowex H^+/MeOH, (ii) *p*TolCOCl/DMAP, (iii) TMSOTf/HMDS/CH_3CN, (iv) NaOMe/MeOH.

Scheme 3. Proposed Mechanism of the Nucleoside Formation from the Pyranose Sugar

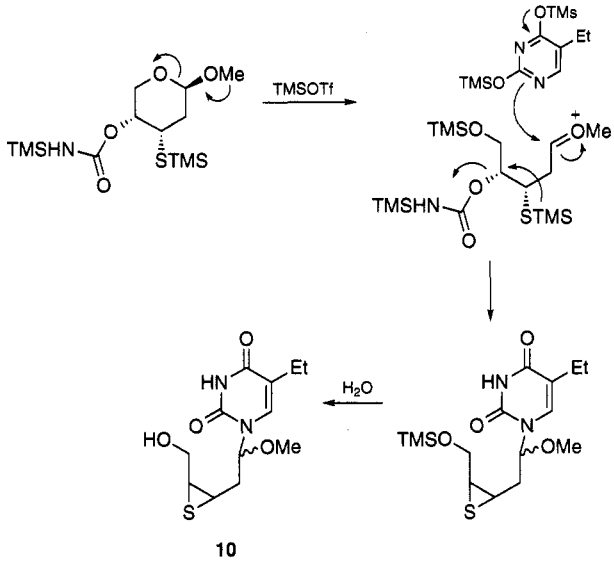


(KBr disc) cm^{-1} 2924, 1732, 1065. Anal. $C_7H_{10}O_4S$ requires C 44.2%, H 5.3%, found C 44.12%, H 5.38%. Mp 98–100 °C.

Methyl 3-*O*-Carbamoyl-2-deoxy-4-thio-β-D-ribopyranoside (4a) and Methyl 4-*O*-Carbamoyl-2-deoxy-3-thio-β-D-ribopyranoside (4b). To the mixture of **3a** and **3b** (6.57 g, 34.6 mmol) was added 10% ammoniacal MeOH (50 mL) and the reaction heated to 50 °C for 2h. The MeOH was removed under reduced pressure to give crude products (6.98 g, 97%) as a 60/40 mixture of isomers which can be readily separated by chromatography to give **4a** as a gum: ^1H NMR (200 MHz, $CDCl_3$) ppm 1.66 (1H, d, J = 8.3 Hz), 1.81 (1H, m), 2.19 (1H, ddd, J = 13 Hz, 7.5 Hz, 3 Hz), 3.41 (4H, m), 3.62 (2H, dd, J = 12 Hz, 6 Hz), 4.7 (3H, m, 1-H), 5.16 (1H, m). MS (EI) m/z 206, 175, 146, 128, 113. IR (film) cm^{-1} 3474, 3556, 1717, 1609. Anal. $C_7H_{13}NO_4S$ requires C 40.5%, H 6.28%, N 6.76%, found C 40.69%, H 6.40%, N 6.54%. **4b** as a white solid. Mp 141–143 °C. ^1H NMR (360 MHz, $CDCl_3$) ppm 1.68 (1H, d, J = 9.6 Hz), 2.96 (2H, m), 3.35 (3H, s), 3.41 (1H, m), 3.78 (1H, dd, J = 12.5, 2.1 Hz), 3.85 (1H, dd, J = 12.7, 1.4 Hz), 4.70 (1H, bs), 4.81 (2H, bs). MS (FAB) 230 $[M + Na]^+$, 208 $[MH]^+$. Anal. $C_7H_{13}NO_4S$ requires C 40.5%, H 6.28%, N 6.76%, found C 40.46%, H 6.15%, N 6.47%.

3'-*O*-Carbamoyl-2'-deoxy-5-ethyl-4'-thiouridine (8). To **5a** (400 mg, 1.93 mmol) in CH_3CN (4 mL) were added HMDS (449 mL, 2.12 mmol) and a crystal of ammonium sulfate, and the mixture was heated under reflux until a clear solution resulted (1 h). The solution was added dropwise over 1 h to a mixture of the bis(trimethylsilyl)-5-ethyluracil and (trimethylsilyl)trifluoromethane sulfonate (TMSOTf) (373 mL, 1.93 mmol) in CH_3CN (10 mL) at 50 °C. The reaction was stirred

Scheme 4. Proposed Mechanism of Thiiarane Nucleoside Formation



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for 1 h and cooled to 10–20 °C, water (0.5 mL) was added followed by amberlite IRA93 (basic resin) (1 g, ~5 mequiv), and the reaction was stirred overnight. The resin and the precipitated 5-ethyluracil were filtered off and the solvents removed under reduced pressure to give a residue. The residue was taken up in THF (5 mL), any further preciptated 5-ethyluracil was removed by filtration, and the solvent was removed to give a crude residue. The crude product can be flash chromatographed (2%MeOH/EtOAc) to give a 1:1 mixture of α and β nucleosides, yield 0.330 g (54%). Crystallization from CH_3CN gives the β-anomer, mp 209–211 °C. **8:** ^{1}H NMR (200 MHz, DMSO-d_6) ppm 1.05 (3H, t, 7.5 Hz), 2.17–2.47 (4H, m), 3.43 (1H, bt, J = 5.8 Hz), 3.65 (2H, bt, J = 6.4 Hz), 5.26 (2H, bm, 3'-H), 6.33 (1H, dd, J = 9.5 Hz, 6.8 Hz), 6.60 (2H, m), 7.81 (1H, s), 11.30 (1H, bs). MS (FAB) m/z 316 (M + 1), 255, 232, 181. Anal. $C_{12}H_{17}N_3O_5S$ requires C 45.71%, H 5.39%, N 13.33%, found C 45.38%, H 5.35%, N 13.27%.

Methyl 3-*O*-carbamoyl-2-deoxy-4-thioribofuranoside (5). To **4a** (4.1 g; 19.8 mmol) in MeOH (50 mL) was added Dowex 50W-X8 resin (4 g), and the mixture was stirred under reflux for 4 h. The Dowex was removed by filtration and the solution concentrated to give a crude solid, which was flash chromatographed using 10% MeOH/$CHCl_3$ to give (2.1 g, 10.1 mmol, 51%) of a mixture of anomers of **5**. Mp 110–116 °C. ^{1}H NMR (200 MHz, $CDCl_3$) ppm 2.31–2.83 (4H, m), 3.31 (3H, s), 3.34 (3H, s), 3.50–3.80 (3H, m, 4-H) 4.60–4.90 (3H, bd), 5.05 (1H, dd, J = 5.3 Hz, 2.5 Hz), 5.14 (1H, dd, J = 3 Hz, 1.5 Hz), 5.27 (1H, m), 5.39 (1H, m). MS (EI) m/z 146 (100%), 128, 113. Mp 110 –116 °C. Anal. $C_7H_{13}NO_4S$ requires C 40.58%, H 6.28%, N 6.76%, found C 40.39%, H 6.43%, N 6.54%.

Methyl 3-*O*-Carbamoyl-2-deoxy-4-thio-5-*O*-*p*-toluoyl-D-ribofuranoside (6). To **5** (15 g, 72.0 mmol) in CH_2Cl_2 (75 mL) and pyridine (75 mL) was added *p*-toluoyl chloride (10.5 mL, 12.32 g, 80.0 mmol), and the mixture was stirred at room temperature for 1 h. The volatiles were removed under reduced pressure and the residue was taken up in CH_2Cl_2 (400 mL) and washed with brine (containing 3% HCl). Workup gave an oil (28.15 g) which was flash chromatographed (silica) using 1% MeOH/$CHCl_3$ to give **6** as mixture of α and β anomers. α-Anomer: ^{1}H NMR (200 MHz, $CDCl_3$) ppm 2.41-(3H, s), 2.49 (1H, m), 3.33 (3H, s), 3.92 (1H, td, J = 6.8 Hz, 2.8 Hz), 4.34 (2H, dd, J = 6.5 Hz, 1.3 Hz), 4.70 (2H, bs), 5.18 (1H, q, J = 5.3 Hz, 2.5 Hz), 5.38 (1H, m), 7.23 (2H, d, J = 8.3 Hz), 7.94 (2H, d, J = 8.3 Hz). Mp 116–118 °C. MS (EI) m/z 294, 265, 233, 129, 119. Anal. $C_{15}H_{19}NO_5S$ requires C 55.38%, H 5.84%, N 4.30%, found C 55.13%, H 5.85%, N 4.23%. β-Anomer: ^{1}H NMR (200 MHz, $CDCl_3$) ppm 2.39 (4H, m, 2-H), 2.62 (1H, ddd, J = 5.5 Hz, 2.8 Hz), 3.30 (3H, s), 3.76 (1H, m), 4.43 (2H, m), 4.62 (2H, bs), 5.12 (1H, dd, J = 5.3 Hz, 3 Hz), 5.50 (1H, dt, m), 7.23 (2H, bd, J = 8 Hz), 7.96 (2H, bd, J = 8.3 HzH). MS (FAB), m/z 264, 189, 146, 128, 119 (100%). Anal. $C_{15}H_{19}NO_5S$ requires C 55.38%, H 5.84%, N 4.30%, found C 55.20%, H 5.88%, N 4.15%.

3'-*O*-Carbamoyl-2'-deoxy-5-ethyl-4'-thio-5'-*O*-*p*-toluoyluridine (7). To the mixture of anomers **6** (16.2 g, 50 mmol) and bis(trimethylsilyl)-5-ethyluracil in CH_3CN/CH_2Cl_2 (100 mL/ 160 mL) at –20 °C was added TMSOTf (11.8 g, 50 mmol) dropwise. The mixture was warmed to room temperature and then heated at 50 °C for 4 h. To the mixture at 0 °C was added sat. aq $NaHCO_3$ (200 mL) slowly with stirring. The precipitated 5-ethyluracil was filtered and washed with CH_2Cl_2 (200 mL). The filtrates were separated, and the organic phase was washed with sat. aq $NaHCO_3$ and dried (Na_2SO_4) to give a solid (19.53 g). The crude product was flash chromatographed using 5% MeOH/$CHCl_3$ to give an α/β mixture of **7** (10.28 g, 48%, 96% based on recovered starting material). ^{1}H NMR (200 MHz, $CDCl_3$) ppm 1.05 (3H, t, J = 7.5 Hz), 1.17 (3H, t, J = 7.5 Hz), 2.15–2.25 (12H, m), 2.60 (1H, ddd, J = 15 Hz, 6 Hz, 2 Hz), 2.76 (1H, ddd, J = 15 Hz, 7 Hz, 5 Hz), 3.89 (1H, m), 4.14 (1H, m), 4.39 (1H, m), 4.53 (1H, bd, J = 6.8 Hz), 4.72 (2H, bs), 4.85 (2H, bs), 5.39 (1H, m), 5.46 (1H, m), 6.35 (1H, dd, 6.3 Hz, 3 Hz), 6.56 (1H, dd, J = 9.5 Hz, 6.3 Hz), 7.26 (4H, m), 7.42 (1H, s), 7.75(1H, s), 7.94 (4H, m), 8.54 (2H, bs). MS (FAB), m/z 434 (M + 1), 418, 373, 298. Anal. $C_{20}H_{23}N_3O_6S \cdot 0.1CHCl_3$ requires C 54.2%, H 5.23%, N 9.43%, found C 54.37%, H 5.29%, N 9.28%.

2'-Deoxy-5-ethyl-4'-thiouridine (9). To **7** (200 mg, 0.46 mmol) in dry MeOH (2 mL) was added sodium methoxide (0.17 mL, 0.92 mmol of a 5.4 M solution) at –10 °C, and the mixture was heated to 50 °C for 5 h. The reaction was cooled and stirred for 30 min with Dowex 50W-X8 (3 g). The mixture was filtered and concentrated to give a solid which was flash chromatographed (10% MeOH/$CHCl_3$) to give 117 mg (0.44 mmol, 93%) of a 1:1 mixture of anomers which can be crystallized from ethanol to give **9**. Mp 206–207 °C. ^{1}H NMR (200 MHz, DMSO-d_6) ppm 1.05 (3H, t, J = 7.5 Hz), 2.22 (4H, m), 3.32 (1H, m), 3.62 (2H, t, J = 5.3 Hz), 4.35 (1H, m), 4.86 (1H, t, J = 5.5 Hz), 4.96 (1H, d, J = 5.3 Hz), 6.26 (1H, t, J = 7.3), 7.73 (1H, s), 10.91 (1H, bs). MS (FAB) m/z 273 (M + 1), 141. Anal. $C_{11}H_{16}N_2O_4S$ requires C 48.53%, H 5.88%, N 10.29%, found C 48.16%, H 6.17%, N 10.29%. CD spectrum in 10% ethanol:water gave ΔE = –5.5 at 263 nm.

3'-O-Carbamoyl-2'-deoxy-4'-thio-5-ethyluridine (8) (from 4a). To **4a** (430 mg, 1.22 mmol) was added HMDS (20 mL), and the mixture heated at 80 °C for 2 h. The HMDS was removed under reduced pressure to give an oil. To the oil in CH_3CN (20 mL) at 0 °C were added bis(trimethylsilyl)-5-ethyluracil solution in CH_3CN (2.44 mL, 2.44 mmol) and TMSOTf (288 mg, 0.244 mL, 1.22 mmol), the solution was heated to 50 °C for 2 h, a further 0.5 equiv (0.12 mL) of TMSOTf was added, and the mixture was heated for 2 h. The mixture was cooled to 0 °C, aqueous pyridine (0.59 mL, 7.32 mmol) was added, and the precipitated 5-ethyluracil was removed by filtration. The filtrate was stirred with a basic resin (Amberlite IRA 93) for 30 min, filtered, and concentrated. The residue was taken up in water and filtered, stirred with Dowex 50W H^+ resin, filtered, and concentrated to give **8** (250 mg, 0.58 mmol, 47%) as a mixture of anomers.

2'-Deoxy-5-ethyl-4'-thiouridine (9) (from 8). **8** (200 mg, 0.46 mmol) was treated with sodium methoxide as for the preparation of **9** from **7** to give **9** (112 mg, 0.36 mmol, 77%).

1-[2-[2-(Hydroxymethyl)thiiaran-1-yl]-1-methoxyethyl]-5-ethyluracil (10). Following the method described for the preparation of **8** above using **4b** (1.0 g, 4.8 mmol) was isolated **10** (250 mg, 0.8 mmol, 18%) as a colorless glass as a mixture of epimers. Mp 41–43 °C. ^{1}H NMR (200 MHz, DMSO-d_6), ppm, 1.03 (6H, m), 1.60 (1H, m), 2.0 (1H, m), 2.25 (1H, m), 2.25 (6H, m), 2.50 (1H, m), 2.55 (1H, m), 2.74 (1H, m), 2.83 (2H, m), 3.21 (3H, s, OMe), 3.23 (3H, s), 3.41 (2H, m), 3.47 (2H, m), 5.60 (2H, m), 7.28 (1H, s), 7.48 (1H, s). The assignments were made using a combination of 2D COSY and ^{13}C(DEPT) studies. MS (EI) 286 (M^+), 271, 211, 147, 140. Accurate mass for $C_{12}H_{18}N_2O_4S$ calculated 286.09873, found 286.10128. Anal. $C_{12}H_{18}N_2O_4S$ requires C 50.34%, H 6.29%, N 9.97%, found C 50.36%, H 6.59%, N 9.87%.

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